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ASSOCIATION OF PHYSICAL ACTIVITY ON PERFORMANCE, QUALITY OF LIFE AND TELOMERE LENGTH IN OLD AGE

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DOCTORAL DISSERTATION

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LIST OF ORIGINAL PUBLICATIONS

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III. Jantunen H, Wasenius N, Salonen MK, Kautiainen H, von Bonsdorff MB, Kajantie E, Eriksson JG. Change in physical activity and health-related quality of life in old age – a 10-year follow-up study. Scandinavian Journal of Medicine & Science in Sports, 2019;29(11):1797-1804.

IV. Jantunen H, Wasenius N, Maria Angela Guzzardi, Patricia Iozzo, Salonen MK, Kautiainen H, Kajantie E, Eriksson JG. Physical activity and telomeres in old age – a longitudinal 10-year follow-up study. Gerontology, published online 2020

The publications are referred to in the text by their roman numerals.

ABSTRACT

As people live longer, enabling older people to live independently and successfully perform everyday activities has become an important issue. In old age, maintaining adequate level of physical functioning is one of the primary determinants of quality of life. The decline in cardiovascular, metabolic and musculoskeletal function with age is likely to be mediated in part through a reduction in physical activity. By engaging in regular exercise, it is possible to counteract several age-related changes. The aim of this thesis was to explore the association between physical activity on healthy active aging by applying measures of physical performance, health-related quality of life (HRQoL) and leucocyte telomere length (LTL) in older age.

The subjects in this study belong to the clinical study cohort (n=2003) of the Helsinki Birth Cohort Study (HBCS). Studies I and II include 695 individuals who attended a clinical examination between the years 2011 and 2013. Study III includes 1036 individuals and study IV 1014 individuals who took part in both clinical examinations in 2001-2004 and 2011-2013. The volume of physical activity was measured both with activity monitors (in study I and II) and through questionnaires (study III and IV). Physical performance was assessed with a Senior Fitness Test, HRQoL with Short Form-36 (SF-36) questionnaire and relative LTL was measured with a quantitative PCR.

In this aging study cohort objectively measured total daily physical activity was associated with physical performance tested with the Senior Fitness Test (SFT). Both light physical activity and moderate to vigorous physical activity (MVPA) were positively associated with the overall SFT score. When the study group was divided by weight at birth, the association between physical activity and physical performance was most obvious among men with low birth weight. Increasing leisure-time physical activity (LTPA) over a 10-year follow-up was positively associated with better physical component of HRQoL in both men and women. In women, there were also a significant association between positive change in LTPA with change in the mental component of HRQoL and with less depressive symptoms. At baseline, volume of LTPA was not

associated with LTL in men or in women. But in women, during the 10-year follow-up a higher volume of LTPA at baseline was associated with greater shortening of LTL.

Our findings support the importance of regular physical activity among older adults because of its positive influence on physical performance and HRQoL to promote physical independence and health maintenance and compress morbidity. According to our findings influences during prenatal life might have long-term effects on health. Physical activity may have a sex-specific role in regulation of telomere length in the aging process.

TIIVISTELMÄ

Eliniän pidetessä tärkeäksi kysymykseksi niin yksilön kuin yhteiskunnan kannalta muodostuu, miten iäkkäät säilyttävät itsenäisyytensä, pärjäävät kotona ja selviytyvät arkipäivän askareista. Ikääntyessä riittävä fyysinen toimintakyky on yksi tärkeimmistä hyvän elämänlaadun edellytyksistä. Iän mukana tuomat sydän- ja verisuonitoiminnan heikkeneminen, metaboliset muutokset ja lihas- ja tukirankatoiminnan heikkeneminen johtuu osittain vähentyneestä fyysisestä aktiivisuudesta. Sen vuoksi säännöllinen liikunta voi ehkäistä osaa vanhenemiseen liittyvistä muutoksista. Tämän tutkimuksen tarkoitus oli selvittä fyysisen aktiivisuuden yhteyttä fyysiseen toimintakykyyn, elämänlaatuun ja leukosyyttien telomeeripituuteen vanhemmalla iällä.

Tutkittavat kuuluvat Helsinki syntymäkohorttitutkimuksen (HBCS) kliiniseen tutkimusjoukkoon (n=2003). I ja II osajulkaisussa on mukana 695 tutkittavaa, jotka osallistuivat toiseen kliiniseen tutkimukseen vuonna 2011-2013. Osajulkaisussa III on mukana 1036 ja osajulkaisussa IV 1014 tutkittavaa, jotka osallistuivat sekä ensimmäiseen että toiseen kliiniseen tutkimukseen vuosina 2001-2004 ja 2011-2013. Fyysinen kokonaisuusaktiivisuus on mitattu sekä aktiivisuusmittarilla (osajulkaisu I ja II) sekä kyselylomakkeella (osajulkaisu III ja IV). Fyysistä toimintakykyä mitattiin Senior Fitness Test:llä (SFT), terveyteen liittyvää elämänlaatu Short Form-36 (SF-36) –kyselyllä ja suhteellinen leukosyyttien telomeeripituus kvantitatiivisella polymeraasiketjureaktiolla.

Tässä ikääntyvässä tutkimusjoukossa objektiivisesti mitattu päivittäinen fyysinen kokonaisaktiivisuus oli yhteydessä SFT:llä mitattuun fyysiseen toimintakykyyn. Sekä kevyt että reipas ja rasittava fyysisen aktiivisuuden määrä oli positiivisesti yhteydessä SFT:een kokonaistulokseen. Kun sekä miehet että naiset jaettiin ryhmiin syntymäpainon perusteella, fyysisen aktiivisuuden yhteys fyysiseen toimintakykyyn oli selvin pienipainoisina syntyneillä miehillä. Vapaa-ajan fyysisen aktiivisuuden määrä lisääminen kymmenen vuoden seurannan aikana oli positiivisesti yhteydessä terveyteen liittyvän elämänlaadun fyysiseen komponenttiin sekä miehillä että naisilla.

Naisilla vapaa-ajan fyysisen aktivisuuden määrän lisääminen oli myös yhteydessä parantuneeseen psyykkiseen terveyteen liittyvän elämänlaadun komponenttiin ja vähentyneisiin masennusoireisiin. Lähtövaiheessa vapaa-ajan fyysisen aktiivisuuden määrä ei ollut yhteydessä leukosyyttien telomeeripituuteen miehillä eikä naisilla. Naisilla kuitenkin 10-vuoden seurannan aikana korkeampi lähtötason vapaa-ajan fyysisen aktiivisuuden määrä oli yhteydessä suurempaan leukosyyttien telomeeripituuden lyhenemiseen.

Löydöksemme tukevat vanhenevan väestön säännöllisen fyysisen aktiivisuuden tärkeyttä. Sillä on positiivinen yhteys fyysiseen toimintakykyyn, parempaan terveyteen liittyvään elämänlaatuun ja tätä myötä fyysisen itsenäisyyden ja terveyden säilymiseen ja sairastavuuden vähenemiseen. Löydöstemme perusteella syntymää edeltävällä ajalla voi olla kauaskantoisia vaikutuksia terveyteen ja fyysisellä aktiivisuudella voi olla sukupuolesta riippuvainen vaikutus telomeeripituuteen.

ABBREVIATIONS

^{18}O	Stable isotope of oxygen
^{2}H	Deuterium (stable isotope of hydrogen)
AEE	Activity energy expenditure
ATP	Adenosine triphosphate
BDI	Beck's Depression Inventory
BMI	Body mass index
CI	Confidence interval
CO_2	Carbon dioxide
CVD	Cardiovascular disease
DHEA	Dehydroepiandrosterone
DLW	Double labelled water
DOHaD	Developmental origins of health and disease
EE	Energy Expenditure
EWGSOP	European Working Group on Sarcopenia in Older People
FEV_1	Forced expiratory flow rate over one second
FISH	Fluorescence in situ hybridization
FVC	Forced vital capacity
GH	Growth hormone
HBCS	Helsinki Birth Cohort Study
HRQoL	Health-related quality of life
IGF-1	Insulin-like growth factor-1
kcal	Kilocalorie
KIHD	Kuopio Ischaemic Heart Disease Risk Factor
kJ	kilojoule
LT	Leucocyte telomere
LTL	Leucocyte telomere length
LTPA	Leisure-time physical activity
MCS	Mental component summary
MET	Metabolic equivalent of task
METh	MET-hours

METmin	MET-minutes
mtDNA	Mitochondrial DNA
MVPA	Moderate to vigorous physical activity
NCD	Non-communicable disease
NEAT	Non-exercise activity thermogenesis
O_2	Oxygen
PADL	Performance Test of Activities of Daily Living
PAEE	Physical activity energy expenditure
PAS	Pasieka's Assessment Score
PCR	Polymerase chain reaction
PCS	Physical component summary
PGC-1α	Peroxisome proliferator-activated receptor gamma, coactivator 1 alpha
PGC-1β	Peroxisome proliferator-activated receptor gamma, coactivator 1 beta
PPT	Physical Performance Test
REE	Resting energy expenditure
RMR	Resting metabolic rate
ROS	Reactive oxygen species
RPE	Rating of perceived exertion
RQ	Respiratory quotient
RV	Residual volume
SD	Standard deviation
SF-36	Short Form-36
SFT	Senior Fitness Test
SPPB	Short Physical Performance Battery
SPSS	Statistical package for social sciences
SWA	SenseWear Armband
T(E)RF	Telomere repeat binding factor
TEE	Total energy expenditure
TEF	Thermic effect of food
Terc	Telomerase RNA component
Tert	Telomerase reverse transcriptase

TL	Telomere length
TLC	Total lung capacity
TRF	Telomere restriction fragment
VC	Vital capacity
VO_2	Oxygen consumption
VO_2max	Maximum oxygen uptake
WHO	World Health Organization

1 INTRODUCTION

The proportion of people aged 65 years and above is globally rapidly increasing. It is estimated that in Finland over one fourth (26 %) of Finnish residents will be aged 65 or over in year 2030 (2). The life expectancy is increasing and the largest increase is seen in the oldest old subgroup (those aged ≥80 years) (3). Aging increases heterogeneity within the age group and subsequently physical functioning and experienced health will become the best indicators of overall situation and prognosis of the individual over age and diseases. In old age, physical functioning plays a key role in preserving independence and coping with activities of daily life and is one of the main determinants of quality of life (4, 5). Preserving adequate physical functioning is becoming an important global health issue.

It is important for individual to maintain and for the society to enable and support independent life as long as possible and diminish the time to live with diseases and functional disability. As people are living longer, the quality of life is also becoming an important issue. It is important to recognize and deal with the risk factors for poor health and performance.

Worldwide cardiovascular diseases are the major causes of death and in high-income countries the most common chronic health conditions are ischemic heart disease, cerebrovascular disease, depressive disorders, and dementias (3). According to the World Health Organisation (WHO), physical inactivity is globally the fourth leading risk factor for mortality (6). Physical activity is a modifiable health behaviour that has a myriad health benefits. Physical activity has shown to be important in maintaining physical functioning and in preventing several chronic non-communicable diseases, such as cardiovascular disease, type 2 diabetes, some cancers, cognitive disorders and depression (7-9).

According to the developmental origins of health and disease (DOHaD) hypothesis, intrauterine and early childhood environmental circumstances can have long-term health consequences later in life and often result in a predisposition to age-related system decline (10). Many of these factors have

been recognised including an unhealthy diet, lack of exercise, smoking, alcohol, stress and environmental pollutants (11-15). One of the earliest proponents of the theory of fetal origins of adult disease was David Barker, who showed that prenatal undernutrition was associated to coronary heart disease (16). Birth size serves as a marker of adverse intrauterine environment and low birth has been associated with all-cause mortality, an increased risk of developing type 2 diabetes, decreased muscle strength, lower health-related physical functioning and with lower LTPA in late life (17-21).

As people are living longer, the quality of that longer life becomes a central issue. Despite suffering from chronic conditions, elderly individuals can have a good level of health and remain capable of common daily activities. One of the health challenges is to increase the number of healthy years. Health-related quality of life (HRQoL) is a multidimensional concept incorporating physical, mental and social dimensions. It is a subjective measure encompassing satisfaction and wellbeing, how people experience diseases, symptoms and limitations. Physical activity has shown to be positively associated with better HRQoL and reduction in depressive symptoms in older people (22, 23).

The telomeres are a region of repetitive nucleotide sequences at each end of a eukaryotic chromosome. Telomeres stabilize the chromosome during DNA replication (24). They shorten every time the cell replicates and allow the chromosomal DNA to be replicated completely without loss of DNA. When telomeres become critically short, cells become senescent or die (24). Telomeres have been proposed to be biomarkers of aging (25), and shorter telomeres are connected to premature cellular aging (26). Telomeres shorten with age (27), but can also be shortened by stress, smoking, obesity, lack of exercise and a poor diet (28-32). Shorter telomere length is associated with many non-communicable diseases, such as hypertension, coronary artery disease and type 2 diabetes (33-35). Physical activity is associated with many of these chronic conditions. Telomere length could be postulated to be a biomarker of healthy aging as telomere length has been positively associated with number of years of healthy living (36).

Helsinki Birth Cohort Study (HBCS) is a unique birth study, the epidemiological cohort including 13,345 subjects born in 1934-44 in Helsinki, Finland. The cohort has data throughout the life span including prenatal life, early childhood and later life enabling to focus upon the early origins of health and disease from a life course perspective and to study long term health influences. Besides the extensive epidemiological data, over 2000 randomly selected subjects constituted the clinical part of the study. This clinical study cohort has been followed up clinically almost over two decades with extensive data available including metabolic data, dietary information as well as other lifestyle data. This enables unique research of the role of physical activity on different health aspects during later life.

2 REVIEW OF THE LITERATURE

2.1 PHYSICAL ACTIVITY

2.1.1 DEFINITON

Physical activity is defined as any bodily movement by skeletal muscles that requires energy expenditure (37). Physical activity can be categorized into occupational physical activity, commuting physical activity, sleep and leisure-time physical activity (LTPA) (37, 38). LTPA can be further divided into sports, conditioning, household and other activities. Exercise is a subcategory on LTPA. It is defined as planned, structured and repetitive bodily movements and its objective is to improve or to maintain one or more components of physical fitness (37). Occupational physical activity is work-associated, usually referenced to an 8 hour working day (38). Commuting physical activity refers to physical activity in transportation to and from work.

Total energy expenditure (TEE) is comprised of physical activity energy expenditure (PAEE), resting energy expenditure (REE) and the thermic effect of food (TEF) (39). Physical activity is a behaviour that results in an elevation of energy expenditure above resting levels. Physical activity induced energy expenditure is the most variable component of TEE as it varies largely between individuals. It usually accounts for 15-30 % of daily energy expenditure (40). Energy expenditure associated with physical activity varies between person to person and it depends on the intensity, duration and frequency of physical activity. PAEE includes the energy expended in volitional physical activity, such as exercise, and nonvolitional activity, such as spontaneous muscle contractions, maintaining posture and fidgeting. Differences in spontaneous minor activity can alter PAEE as much as 20 % (41). PAEE depends on body movement and also on body size. Greater energy is required to move a larger body (39). Physical activity level also depends on age. Activity related energy expenditure increases from 20% at age one to ~35% at age 18 and seems to be highest at reproductive age and often declines after age 50 (39). The lower

activity energy expenditure of children might be due to the fact that it takes less energy to move around with a lower body weight (39). Exercise training interventions have shown to induce an increase in physical activity after exercise in young but not in older individuals (39). The lack of an effect of exercise training on total daily physical activity in elderly is explained by a compensatory reduction of spontaneous physical activity or non-exercise activity thermogenesis (NEAT) (42). NEAT means the energy expended for everything when not sleeping, eating or sports-like exercise (43). It is the energy expenditure associated with spontaneous, non-exercise physical activity and includes the energy expenditure e.g. of walking to work, typing, performing yard work, undertaking agricultural tasks and fidgeting.

Sixty to 75 % of TEE is constituted by resting energy expenditure (REE) (44). REE is a result of energy expended during normal cellular and organ function under postabsorvative resting conditions. Resting metabolic rate (RMR) plays a central role in the regulation of energy balance. Factors influencing RMR include age, body composition, nutritional state, thyroid function and sex (44). With age RMR declines and this is mainly due to decline in fat-free weight, but also due to decline in cardiorespiratory capacity (45). The age-related decline is gender dependent what comes to the rate and onset of the decline in RMR (44). RMR and changes in RMR to exercise training has shown to have a genetic influence (46, 47).

Diet-induced thermogenesis, the thermic effect of food (TEF), constitutes 5-15 % of total daily energy expenditure (48). TEF means the increment in energy expenditure after a meal and includes the energy production in the body caused by metabolizing the food ingested including the energy expended in digestion, absorption and sympathetic nervous system activation. The main determinant of diet-induced thermogenesis is the amount of ingested food, the energy content, but it also varies due to the composition of food (49). Values are highest for protein and alcohol fraction of the diet and lower at a high fat and carbohydrate consumption (48). The thermic response to meal has been shown to be more influenced by the level of physical activity than age and shown to be greater with individual with high maximum oxygen uptake (VO_2max) (44, 49).

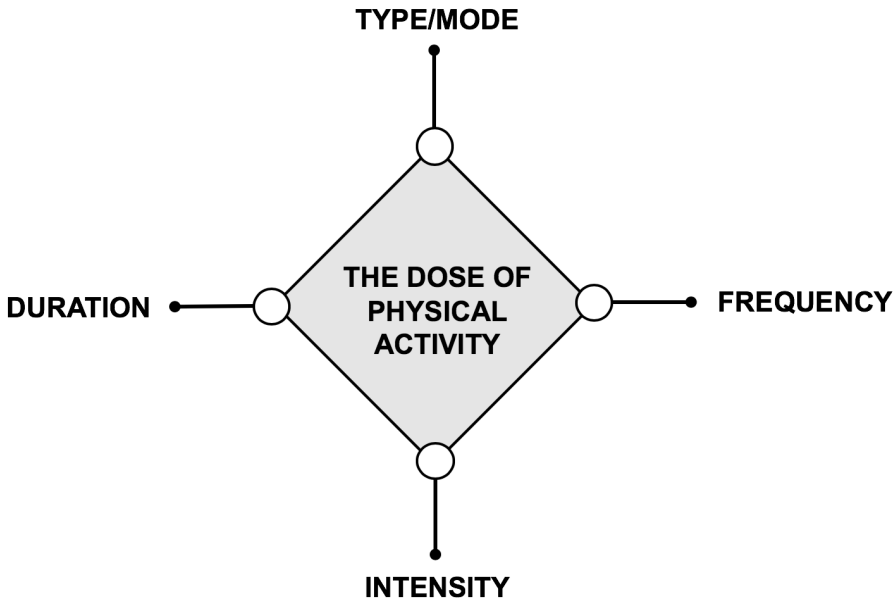

Figure 1 Characteristics of physical activity.

2.1.2 DETERMINANTS OF PHYSICAL ACTIVITY

Determinants of physical activity can be categorized as personal, environmental and characteristic of the activity (50) (Figure 2). The characteristics of physical activity includes the intensity, duration and frequency and mode/type of the activity (38) (Figure 1). Intensity can be described in many ways. It can be rated as perceived exertion (RPE values) commonly based on Borg's scale 6-20 (51). The intensity of physical activity can be described in relative terms, for example in percentage of maximal oxygen uptake, oxygen uptake reserve, heart rate reserve and maximal heart rate. It can also be reported as the absolute intensity of physical activity, that is the actual rate of energy expenditure. It can be expressed as oxygen uptake (L/min or mL/kg/min), in kilojoules (kJ) or kilocalories (kcal) or in METs

(Metabolic Equivalent of Task). Energy expenditure can be measured in kJ or in kcal. One kcal equals to 4.184 kJ. MET is the ratio of metabolic rate (and the rate of energy consumption) during a specific physical activity to a reference metabolic rate. One MET equals to the resting metabolic rate obtained during quiet sitting. One MET is equivalent to oxygen consumption of 3.5 ml/kg/min or 1 kcal/kg/hour. The Compendium of Physical Activities has been developed to standardize the assignment of MET intensities (52). MET values of activities range from 0.9 while sleeping to 23 running at 22.5 km/h pace. Based on the recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine for physical activity and public health by Pate et al. (53) MET values under 3 are defined as light, 3-6 as moderate and over 6 as vigorous intensity activity. These intensity categories are usually used among healthy adults aged 18 to 65 years for promoting and maintaining health.

The value equating 1 MET (3.5 ml/kg/min) was first derived from the resting O_2 consumption of one person, a 70-kg, 40-yr-old man with a surface area of 1.8 m^2 (54). Since the resting metabolic rate depends on the subject's lean body mass, age, health status and environmental factors, the actual resting metabolic rate may differ from 3.5 ml/min/kg. Resting metabolic rate measurements by calorimetry has shown that the conventional 1-MET value may overestimate the actual O_2 consumption and energy expenditure especially in obese and elderly individuals (55).

The volume of physical activity expresses the absolute intensity, duration and frequency of physical activity. The volume of physical activity in kcal in specific time frame (for example kcal/week) can be calculated by multiplying the weight of the subject, frequency, duration of the physical activity and the intensity for the physical activity in kcal. However, in physical activity research the volume of physical activity is usually expressed in MET-minutes (METmin) or in MET-hours (METh). METmin or METh is calculated by multiplying the intensity of performed physical activity in METs with the duration (in minutes or hours) and frequency of the activity.

The frequency of physical activity is often described as the number of activity sessions per day or week. When examining the stability of physical

activity for longer time periods, the frequency can also be reported monthly or yearly. The duration of physical activity refers to the number of minutes of the activity session. The duration of occupational physical activity is often defined as 8 hours.

Personal characteristics that can have an influence on physical activity participation include past or present knowledge, attitudes, behaviours, personality characteristics, biomedical traits, demographic factors and predisposition (39, 50). For example, physical activity level already in preschool age has shown to predict physical activity level in adulthood (56). In addition, less-educated, smokers and overweight persons are less likely to engage in exercise (57, 58). Physical activity level increases from age one to reach adult values by about the age of 15 years (59). Physical activity level of an 18-year old subject does not differ form a 50-year subject and after age 50 physical activity on average declines (39).

Both social and physical environmental factors can help or hinder participating in physical activity. Social environmental factors include the attitudes of family and friends (60) and, also the recommendations of physicians. Physical environmental factors influencing the physical activity level can be for example weather, access to facilities, enrolment fees and time pressure.

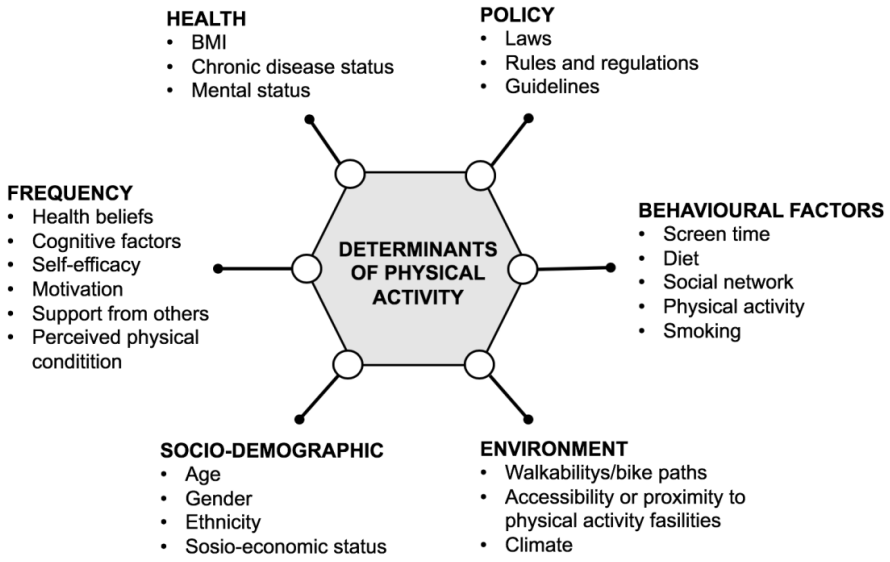

Figure 2 Socio-environmental determinants of physical activity.

2.1.3 METHODS OF MEASUREMENTS

Physical activity can be measured in many ways. It can be self-reported, measured with heart-rate monitors and other portable devices or more accurately measured with calorimetry. The chosen method depends on the accuracy and feasibility of the method, sample size, age of the participants, assessment time, type of information needed and costs.

2.1.3.1 Calorimetry, indirect calorimetry and double labelled water

Direct calorimetry measures the energy expenditure by measuring the heat production or heat loss emitted from the body surface. It is the most accurate method to measure metabolic rate in living organisms (61). Metabolic rate equals the metabolic heat production if any mechanical work does not occur. The first calorimeters to measure human energy expenditure were direct calorimeters, but nowadays they have mostly been replaced by less demanding indirect calorimetry.

Indirect calorimetry calculates heat production or loss by measuring oxygen consumption and/or carbon dioxide production. Resting and basal metabolic rate can be measured with indirect calorimetry. It also allows the identification of energy substrates based on the respiratory quotient. Respiratory quotient (RQ) is the ratio of the CO_2 production and O_2 consumption in the tissue measured directly from blood. Measuring the respiratory exchange ratio (RER) is a non-invasive alternative method to measure the exchange ratio from carbon dioxide production (Vco2) and oxygen consumption (Vo2) from gas exchange measurements. RQ value of 0.7 indicates 100 % fat metabolism whereas 1.0 is assumed to indicate pure carbohydrate metabolism. The measured VO_2 can be converted to calories based on the formula 4.69 kcal/litre of O_2 when RQ equals 0.707 and 5.05 kcal/l O_2 when RQ equals 1.0 (62).

The double labelled water (DLW) method is regarded as the golden standard of measuring energy expenditure in free-living individuals and to validate techniques of estimating physical activity levels (63). DLW usually uses orally administered water labelled with isotopes of ^{2}H and ^{18}O. ^{2}H is eliminated as water and ^{18}O is eliminated as both water and carbon dioxide. The production of carbon dioxide can be measured by the difference between the elimination rate of these two isotopes. The double labelled water method can be used in free living humans to measure energy expenditure in their normal surroundings for a time period of a couple of days to several weeks. The optimal observation period is 1-3 biological half-lives of the isotopes and the observation interval varies from 1 week in children and endurance athletes to 3 weeks in elderly when measuring energy expenditure under daily living conditions (64, 65). In the beginning of the observation period the participants ingest water labelled with isotopes. During the observation period, they collect body water samples (blood, saliva, or urine). These are analysed by mass spectroscopy and the carbon dioxide production can be calculated by the disappearance of the two isotopes. Validation studies have reported an accuracy of 2-8 % against respiratory gas exchange (64). However, the double labelled water method does not give information on the type, intensity or

duration of physical activities (66). It only gives average total daily energy expenditure during the observation period.

2.1.3.2 Portable devises

The use of a portable heart rate monitor is an objective method to assess physical activity that is based on a strong positive association between heart rate and energy expenditure (67). Energy expenditure is estimated based on the assumption of a linear relationship between heart rate and oxygen consumption (68). Heart rate is shown to be correlated to VO_2 during physical activities (69). Recording heart rate is a low cost, easy, feasible and non-invasive method to measure physical activity, but many factors, such as age, medication and activity level can influence the relationship between heart rate and VO_2 (69). Also, the relationship between heart rate and oxygen consumption differs between upper and lower body activities and the relationship between heart rate and energy consumption is less predictive during light exercises (70).

Motion sensors, such as a pedometer or an accelerometer, are electronic or electromechanical devices that detect or count human movement. Pedometer is a device that counts each step a person takes by detecting the motion of a person's hand or hip. By calibrating the distance of a person's step, the distance walked can be measured. The accuracy of pedometers varies widely and depends on the type of surface walked on, the placement of the device, walking speed and how easily the device counts falsely other movements as steps (71, 72).

Accelerometer-based monitors quantify acceleration of human body resulting from physical activity around one, two or three axes. Accelerometers are inexpensive, easy to use and can give information on the intensity, frequency and duration of physical activity. But they also have some important limitations. The monitor is worn in a fixed position, often over the hip, and thus it is susceptible to miss upper body movements. They can only distinguish a few types of activities and do not capture common activities such as cycling, resistance and static exercise and carrying loads. They also have low sensitivity to sedentary activities (73). Also uniform practise and standards for processing

the data should be introduced (74). A recent review (75) of 134 studies showed moderate validity of accelerometers. The pooled correlations with doubly labelled water were 0.39 (activity energy expenditure) and 0.52 (total energy expenditure) for uniaxial devices, and 0.59 and 0.61 respectively for triaxial devices. Uniaxial devices underestimated total energy expenditure by 12 % and triaxial devices by 7 % (75).

As no single technique is able to catch all aspects of physical activities in free-living conditions, more complex hybrid devices have been invented. The SenseWear Armband (SWA) is an example of a such multisensory body monitor. It is worn on the triceps of the arm and it measures skin temperature, near-body temperature, heat flux, galvanic skin response, and biaxial accelerations. The information of these physiologic parameters is combined with an individual's demographic characteristics (sex, age, height and weight) and analysed using a computer software to provide minute-by-minute estimates of energy expenditure. It has shown to provide valid estimates of energy expenditure both at rest (r = 0.76) and during exercise (r = 0.47-0.69) compared to indirect calorimetry (76) and the energy expenditure estimated by the SWA also correlates strongly with estimates from doubly labelled water in free-living conditions (77).

2.1.3.3 Subjective measures of physical activity

Individual recordings of physical activity can be by self-reported questionnaires, self-reported activity diaries/logs or by interviews. Subjective methods to assess physical activity also include direct observation. Questionnaires are the most common method to assess physical activity. They are inexpensive, easily available, non-invasive, can be used in studies involving a large number of participants and can determine categories of activity level. The shortcomings of questionnaires include that they have limited reliability and validity (78) and how the data derived from the questionnaires are converted to units of energy expenditure.

When using self-reported diaries participants must record physical activity in real time and are thus less susceptible to recall bias. Also, self-reported physical activity can be biased by participants' cognitive reporting ability (79).

Self-reported physical activity can give detailed information about the type, purpose, intensity and duration of the activity, but they can be affected by a behaviour change of the participant due to awareness of being observed and diaries tend to be burdensome (80). Behavioural observation is one of the earliest methods to assess physical activity. It is time consuming, expensive and the interpretation of the activity is subjective to the observer.

2.2 AGING

2.2.1 THEORETICAL FRAMEWORK

Aging can be defined as deteriorative changes during postmaturational life that are associated with an increased risk of morbidity, disability and death (3). The process of human aging commences as early as conception and does not cease until death. According to evolutionary biology aging is defined as an age-dependent or age-progressive decline in intrinsic physiological function (81). The underlying physiological state of an individual leads to age-specific mortality rate and age-specific reproductive rate. A gerontologist Bernard Strechler has proposed five criteria for normal aging (82): Ageing is cumulative so that effects of aging increases with time. It is universal; all individuals of a species displaying signs of aging. It is progressive; changes that lead to aging occur progressively throughout the life span. It is intrinsic; the causes that are origin of aging are endogenous. In other words, they must not depend on extrinsic factors. And it is deleterious so that changes occurring compromise normal biological functions.

There are many theories explaining the process of aging. According to the Hayflick limit theory of aging from 1961, the human cells have a limited ability to divide to approximately 50-times, after which they simply stop dividing (83). Modern biological theories of aging fall into two main categories: programmed and damage or error theories (84). According to the programmed theories, aging follows a biological timetable that is regulated by changes in gene expression that affects the systems responsible for maintenance, repair and defence (85). According to damage or error theories cumulative damage caused by environmental factors to living organisms are

the cause of aging (86). The damage theory is also called as non-programmed aging theory and it is based on evolutionary concepts where aging is considered the result of an organism's inability to combat against natural deteriorative processes (87). The disposable soma theory of aging closes the gap between mechanistic and evolutionary theories of ageing by suggesting that ageing results from progressive accumulation of molecular and cellular damage, as a direct consequence of evolved limitations in the genetic settings of maintenance and repair functions (88). The disposable soma theory postulates that there is a trade-off in resource allocation between somatic maintenance and reproductive investment (89). According to this theory organism only has a limited amount of resources or "soma" that it can allocate to its various cellular processes. Therefore, there is a compromise and resources are partitioned accordingly. This compromise is thought to damage somatic repair systems, which can lead to progressive cellular damage and senescence. Therefore, a greater investment in growth and reproduction would result in reduced investment in DNA repair maintenance, leading to increased cellular damage, shortened telomeres, accumulation of mutations, compromised stem cells, and ultimately, senescence (90).

The programmed theory can be divided into three sub-categories (84). The programmed longevity theory considers aging to be the result of a sequential switching on and off certain genes (91). According to the endocrine theory, hormones control the pace of aging. Studies have shown insulin/IGF-1 signalling pathways to have a key role in the hormonal regulation of aging (92). The immunological theory is based on the fact that the immune system is programmed to decline over time and increases vulnerability to infectious diseases and thus aging and death (93). Dysregulated immune response has been associated to cardiovascular disease, Alzheimer's disease, autoimmune disease and cancer (94-96).

The damage or error theory can be divided into five sub-categories (84). According to the wear and tear theory, effects of aging are caused by progressive damage to cells and body systems over time from accidents, diseases, radiation, toxic substances, food, and many other harmful substances when they are utilized for a long time. Bodies "wear out" due to use

and harmful substances and can no longer function correctly. Rate of living theory states that the greater an organism's rate of basal metabolism, the shorter the life span is (97). According to the cross-linking theory, known also as glycosylation theory of aging, binding of glucose to protein makes proteins impaired and unable to perform efficiently (98). The binding of glucose occurs under the presence of sugar. The accumulation of cross-linked proteins damages cells and tissues and this slows down bodily processes resulting in aging (99). The free radicals theory proposes that superoxide and other free radicals cause damage to the macromolecular components of the cell causing cells and eventually organs to stop functioning (100, 101). Diet, lifestyle, drugs and radiation can accelerate free radical production and thus accelerate aging. There are some natural antioxidants in the body to restrain free radicals. The somatic DNA damage -theory proposes that aging results from damage of genetic integrity on body's cells (102). DNA damage is continuously occurring, but most of these damages are repaired by DNA polymerase and other repair mechanisms. Genetic mutations occurring with increasing age can lead to defunct repair mechanism causing cells to deteriorate and malfunction. In particular, damage to mitochondrial DNA might lead to mitochondrial dysfunction (103). The primary function of mitochondria is to promote energy production by respiration. Thus, mutations in mitochondrial DNA or impairments in the regulative signalling pathways can affect longevity.

There also other theories of aging. According to the telomere theory of aging, telomeres shorten every time the cell replicates and eventually become critically short, causing cells to become senescent or die, which eventually results into the death of entire organism (104).

To date there is no consensus on the theory of aging and in fact many of the theories interact with each other and aging is likely to occur as a consequence of many factors, both environmental and genetic. Nowadays mitochondria are believed to have a critical role in aging. In the last years, instead of the classical mitochondrial free radical theory of aging, the major source of mitochondrial DNA mutations is thought to come from replication errors and failure of the repair mechanisms or to be inherited (103). Mitochondria supply most of the energy to the cell in the form of adenosine triphosphate (ATP) and also

involved in other tasks such as signalling, cellular differentiation, and cell death, as well as control of the cell cycle and cell growth. A drop in cellular ATP can lead to cellular apoptosis and cell death. Mitochondria is believed to have a central role in aging (105). During aging, mitochondria's capacity to produce ATP and the number of mitochondria is decreased. The connection between the fact that mitochondrial DNA (mtDNA) mutations are increased during aging, and the aging process itself, is still controversial (106). Mutations can be maternally inherited, or they can originate from defects in replication or in the repair system, or they can form subsequently after exposure to mutagenic agents such as reactive oxygen species (ROS) or UV irradiation (103). Despite the fact that nowadays it seems to be clear that mitochondrial DNA damage and ROS have a role in the aging process, their correlation is still unclear. One hypothesis is that the increase in ROS is a consequence rather than a cause of aging. It have been proposed that ROS are early messengers in a protective stress-response pathway (103). With aging, the increase in cell damage leads to increase in stress-response pathways and a consequent increased generation of ROS.

Recently a new theory of ageing has been proposed. According to this shadowed regulation of developmental pathways -theory of aging, developmental pathways that are epigenetically regulated and known to be crucial during embryogenesis, contribute to stem cell ageing (107). This theory proposes that epigenetic alterations and dysregulation of these pathways might impair the functionality of adult stem cells during ageing which contribute to the development of ageing-associated organ dysfunction and disease (107).

2.2.2 GENETICS, EPIGENETICS AND PROGRAMMING

Ageing is characterized by a progressive decline in physical, mental, and reproductive capacity, as well as an increase in morbidity and mortality. At the cellular level, intrinsic and extrinsic aging factors causes cell senescence that is characterized by DNA damage that affect gene expression and damage repair systems and contributes to cell dysfunction (108). These changes can be caused through genetic and epigenetic mechanisms, which are influenced by

genes, environmental and stochastic factors (109). Defence and repair systems are highly enzyme dependent and the absence or malfunction of a gene necessary for production and activity of these enzymes can lead to accumulation of cell damage.

Mutations in genes that are responsible for the maintenance of the cell and of its basic metabolism are essential in modulating lifespan. Genes involved in DNA repair (110), telomere conservation (111), heat shock response (112), and the management of free radicals' levels (113) are shown to contribute to longevity or in case of reduced functionality, to accelerated senescence. The genes responsible of the maintenance of the cell and of its basic metabolism have been proposed as the main genetic factors affecting the individual variation of the aging phenotype (114).

Family studies have demonstrated that about 25 % of the variation in human longevity is due to genetic factors and it is more important in old age and among males than among females (115, 116). Offspring of long-lived parents has shown to be protected against age-related diseases (117). Studies of human twins has shown most of the variance of life-span be due to individually unique environmental factors (116).

There is increasing evidence that, in addition to genetic factors, age-associated alteration of gene function might also depend on epigenetic factors, for example DNA hypomethylation and promoter hypermethylation (118, 119). According to the classical definition from early 1940s, epigenetics referred to all molecular pathways modulating the expression of a genotype into a particular phenotype (120). Epigenesis in that time referred to the process of cellular differentiation form totipotent stem cells to fully differentiated cells through different cell lines. The definition has been narrowed and in 2008 Cold Spring Harbor meeting defined an epigenetic trait to be a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence (121). This definition of epigenetics can involve the heritability of a phenotype, passed on through either mitosis or meiosis. Epigenetic regulation refers to the biological mechanisms in which DNA, RNA and proteins are chemically or structurally modified, without changing their primary DNA sequence (122). In other words, epigenetic factors alter gene

expression without changing the underlying DNA sequence. It is characteristic for epigenetics that the same genome can show alternative phenotypes, which are based on different epigenetic states. These epigenetic modifications play critical roles in the regulation of numerous cellular processes, including gene expression, DNA replication, and recombination. Epigenetic regulatory mechanisms include, among others, DNA methylation and hydroxymethylation, histone modification, chromatin remodelling, RNA methylation, and regulation by small and long non-coding RNAs (123). In DNA methylation, a methyl group is attached to the DNA molecule at cytosine. This typically turns genes off by affecting DNA accessibility. Also histone modifications (acetylation, deacetylation, methylation and phosphorylation) affects the accessibility of DNA and can result in either an increase or decrease in gene expression (124). Modifications of non-coding RNA can also lead to both gene silence or activation (125).

Alterations in epigenetic patterns during aging is known as epigenetic drift (126). Genomic DNA methylation decreases with age (118) and tend to correlate with age (127). DNA methylation is associated with longevity, and DNA methylation may play a role in regulating life span (128). Epigenetic modifications affect not only the aging process but also its quality (129). Epigenetic modifications are modulated by both genetic background and lifestyle and environmental factors and are correlated with the rate and quality of aging (130).

Epigenetic modifications can be very stable, and passed on to multiple generations (131), but they can also change dynamically in response to specific cellular conditions or environmental stimuli (132). Although the possibility that epigenetic marks can be transmitted down the generation, in the case of DNA methylation the molecular mechanisms involved in the process are still unclear (133). As most genomic DNA methylation is erased during embryonic development (134), the molecular mechanisms other than methylation must participate in the process.

Genomic imprinting is one form of epigenetic inheritance. It refers to the phenomenon where the developmental process leads to the expression of specific genes from only parental origin even though both parents contribute

equally to the genetic content of their offspring (135, 136). Many imprinted genes have a role in regulating fetal growth, but they have also been shown to have important effects on postnatal development, growth and survival, as well as on adult phenotypes (136). Disrupted expression of imprinted genes can cause an imprinted syndrome, e.g. the Prader-Will Syndrome (137). There is also increasing evidence that altered expression of imprinted genes may also be involved in wide range of common diseases, such as intrauterine growth restriction, obesity, diabetes mellitus, psychiatric disorders and cancer (136).

Maternal metabolism during pregnancy, including over- or undernutrition, altered macronutrient composition, obesity, insulin resistance, or diabetes, promotes alterations in the metabolism and health of her offspring. For example, pre-existing or gestational diabetes has been associated with offspring excessive growth, increased adiposity and hypothalamic dysregulation (138). Metabolic phenotypes can be also be transmitted via the paternal lineage independent of genetics (139). In animal models, high-fat feeding of sedentary female mice resulted in impaired glucose tolerance, increased serum insulin concentrations, and increased percent body fat in mice offspring (140). The detrimental effect of the maternal high-fat diet on the metabolic profile of offspring could be ameliorated by maternal exercise before and during gestation (141). A study also done among mice has shown that maternal high-fat diet resulted in reduced physical activity and lower REE in offspring and higher weight in adulthood (142). Another study has shown that in rodents maternal high-fat diet was linked to decreased exercise performance and training efficiency in the offspring (143).

2.2.3 AGING AND BODILY FUNCTIONS

2.2.3.1 Body composition

Excess body fat accumulation begins progressively in early adulthood and actually more young adults nowadays emerge from childhood already obese (144). Body mass index (BMI) increases with age reaching its peak at about age 65–70 years, but waist circumference continues to increase peaking at 75–

80 years of age (144). This indicates loss of muscle mass and risk of sarcopenia in old age. Many cross-sectional and longitudinal studies have observed increases in fat mass and decreases in muscle mass or lean tissue mass in older adults, often in the absence of differences or changes in body weight (145). With increased age also intramyocellular lipids and visceral fat increases and these changes are related to an increased metabolic risk profile and decreased physical functioning (145). A recent study has shown that greater loss of thigh muscle than expected for overall weight change had a higher mortality risk compared to those with relative thigh muscle preservation, suggesting that conservation of muscle mass is important for survival in old age (146).

2.2.3.2 Bone composition

Bone serves mechanical and homeostatic functions and it is a dynamic organ undergoing a continuous self-regeneration process called remodelling. It protects internal organs, allows locomotion and load-bearing and takes part in the calcium homeostasis. The bone marrow is the primary site of new blood cell production and haematopoiesis. Bone mineral density decreases with age and increases the risk for fractures. Bone loss is known as osteopenia and osteoporosis is a condition characterized by the reduced bone mineral density and increased rate of bone loss. The loss of bone mass is known to progress faster in women than in men due to estrogen depletion after menopause (147). The loss of bone mass is also associated with genetics, calcium and vitamin D deficiency, smoking, high alcohol intake and a sedentary lifestyle (148).

2.2.3.3 Muscular strength

Aging leads to a decrease in muscle mass (149). The age-related loss of muscle mass has been called sarcopenia (150, 151), and it has been defined as the loss of skeletal muscle mass, strength and performance that occurs with age. The loss of muscle mass has usually been defined as being 2 SD below the mean muscle mass of younger person. As there are several definitions of sarcopenia there has been a need for a uniform diagnostic criterion for sarcopenia to be

used in clinical practice and in research studies. One widely accepted criterion is from European Working Group on Sarcopenia in Older People (EWGSOP) (152). According to EWGSOP the definition of sarcopenia includes the effects on function as well as including muscle mass and strength and sarcopenia is defined as a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death (152). According to EWGSOP the diagnosis of sarcopenia requires both clinical findings of low muscle mass and low muscle function (low muscle strength or poor physical performance). Diagnostic testing is needed to confirm the presence of deficits in muscle mass and in strength or performance. Sarcopenia has also been addressed an ICD-10 code in October 2016 (153). Sarcopenia can be divided into primary (or age-related) and secondary sarcopenia according to if a cause of the condition can be defined (152). Secondary sarcopenia can be due to immobility, advanced organ failure or inadequate dietary intake. Cachexia can be thought as an underlying condition of sarcopenia and is defined as a metabolic syndrome in which inflammation is the key feature and characterized by loss of muscle mass with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss (154).

The loss of muscle mass results in decrease in strength, metabolic rate and aerobic capacity. This results in impaired functional ability (155). Muscle mass loss is caused by reduced number of muscle fibers and motor units and decline of muscle fiber size (156). Also, the synthesis rate of muscle proteins decreases, and muscle repair capacities are reduced (149, 157). Decreased level of anabolic hormones, such as estrogen and growth hormones and an increase of catabolic factors such as inflammatory cytokines contribute to muscle mass and strength loss (158). Decreased muscle mass is also associated with physical inactivity, mitochondrial dysfunction (159), co-morbidities such as malignancy and malnutrition (160). There is evidence that exercise and nutritional and pharmacological interventions are able to not only reverse sarcopenia but also increase muscle mass and strength and improve function and decrease disability in the elderly (161, 162).

2.2.3.4 Neural function

There is a 40 % decline in the number of spinal cord axons and a 10 % decline in nerve conduction velocity associated with aging and contributing to neuromuscular performance (163). The changes in the central and peripheral nervous system may reduce an individual's ability to activate available musculature. Already in middle age neuronal atrophy of the cerebral cortex including motor cortex occurs. Also, there is a marked loss of myelinated nerve fiber length in the brain white matter (164). With aging there is a decline in the rate of transport of the materials necessary for axonal regeneration leading to inability to regenerate axons (165). Myelin sheaths of nerve fibers may also be affected in old age and this decreases conduction velocity along axons (165). Also in some regions of the nervous system the number of synapses decreases during normal aging (166). These age-related changes in cerebral cortex affects cortico-cortical and cortico-spinal connectivity potentially and leads to impaired muscle strength. Elderly people have reduced motor cortex plasticity (167).

A motor unit comprises a single peripheral neuron and its innervated muscle fibers. Aging is associated with morphological, physiological, and behavioural changes in motor units and the conduction velocities of efferent axons reduces with aging (168).

Aging affects the reaction time to detect the stimulus and information processing to produce the response more than the muscle action time (163). Cardiorespiratory training has been shown to conserve the reaction time in aging people (169).

2.2.3.5 Endocrine function

The decline in secretion of hormones that happens with age of the reproductive system is known as menopause in women and andropause in men, the growth axis as somatopause and axes involving the adrenal gland as adrenopause. The clinical consequences of these changes include reductions in bone, skin and skeletal muscle mass and strength, derangement of insulin signalling, increases in adipose tissue and effects on immune function.

The estrogen production by the ovaries is controlled by a negative feedback mechanism by the hypothalamic-pituitary-gonadal axis. During the fourth or fifth decade of life the alterations in the interaction between the hormones from hypothalamic and anterior pituitary gland and ovaries decreases the estrogen output from the ovaries causing the menopause. The decrease in estrogen levels causes decline in muscle mass and strength (170) and osteoporosis (171).

Changes in the hypothalamic-pituitary-gonadal axis in men occur more slowly and the testosterone levels decline at a rate of about 1% per year from the age of 30–40 years and causes male andropause (172). The decline in testosterone is also associated with decline in muscle mass and strength (170).

Adrenopause refers to the reduced adrenal cortex output of dehydroepiandrosterone (DHEA). DHEA is transformed to androgens and estrogens in several tissues. The skeletal muscle is able to convert DHEA into active androgens and estrogens, and to stimulate insulin-like growth factor-1 (IGF-1) production. The DHEA levels decrease slowly after age 30 years (173). Low DHEAS has been shown to be associated with osteoporosis (174) and higher prevalence of frailty (175) and with worse physical functioning (176). On the other hand a review has reported no benefit of exogenous DHEA on muscle strength and physical function (177).

The gradual decrease of secretion of growth hormone (GH) from the pituitary gland seen with age is called somatopause. GH production declines 14 % per decade after age 30 years. A parallel decrease of circulating level of IGF-1 also occurs. GH and IGF-1 are both stimulators of cell proliferation and the age-dependent decline in these hormones are associated with sarcopenia. The level of IGF-1 has been shown to be associated with muscle mass and strength in elderly (170).

Insulin sensitivity also declines with aging in several tissues. In skeletal muscles this is one cause of sarcopenia and type 2 diabetes is associated with sarcopenia in older adults (178). Ghrelin, a peptide produced mainly in the stomach, modulates energy and glucose homeostasis. It increases appetite, stimulates GH/IGF-1 secretion, prevents muscle atrophy and regulates bone formation (179). A cross-sectional study has shown that elderly individuals

with sarcopenia had significantly lower ghrelin levels than those without sarcopenia, but ghrelin levels of elderly subjects without sarcopenia were not decreased compared with young adults (180).

Endocrine adaptations during earlier life may affect longevity and health in older age. For example, depletion in early nutritional intake have shown to be associated with both shorter lifespan and increased incidence of pathologies such as diabetes and cardiovascular disease, effects mediated by the insulin and IGF-1 pathways (181, 182).

2.2.3.6 Pulmonary function

Pulmonary structure and function change significantly with aging (183). Respiratory muscle strength and chest wall compliance decreases, alveolar ducts and bronchioles dilates and gas exchange surface lessens (184). Reduced pulmonary capillary volume also contribute to the decreased gas exchange capability (185).

Respiratory performance begins to decline after age 30 years (183). The total lung capacity (TLC) does not change significantly with age, but the residual volume (RV) increases with age and these changes leads to an increase in the ratio RV/TLC and to a decrease in vital capacity (VC), the volume of gas expired by maximal expiration after a maximal inspiration (184). Functional residual capacity (FRC) increases with age. The forced vital capacity (FVC) and forced expiratory flow rate over one second (FEV_1) decreases with age, as both are linked to reduced chest wall compliance and expiratory muscle strength (186). Also, the ventilation-perfusion mismatch increases, and the pulmonary diffusing capacity decreases with age (185, 187).

There are alterations in the immune functions in elderly subjects' lungs and the depression of innate immune function leads to persistent low-grade respiratory tract inflammation (188). Also, the cough reflexes and the ventilation responses to hypoxia and hypercapnia are depressed with aging (189, 190). Elderly subjects compensate the age related pulmonary changes (reduction in tidal ventilation) by increasing breathing frequency that maintains the ventilation at same approximate level as in young adults (191). As the pulmonary function does not respond to exercise training, the age-

associated decline in pulmonary function may be the limiting factor for physical activity and VO_{2max} in the elderly (192).

2.2.3.7 Cardiovascular function

Maximal oxygen consumption declines approximately 10 % per decade after age 30 years (193). The most likely explanation for this age-related decrease of VO_{2max} is the reduction of cardiac output with the occupying decrease in maximum heart rate and stroke volume (194, 195). Other factors accounting for the decrease in VO_{2max} are muscle mass loss, increase in body fat and altered pulmonary function (192, 194). Regular physical activity has a strong influence on age-related decrements in cardiovascular function and endurance capacity (196). A study has shown that the age-related decrease in VO_{2max} of master athletes who continue to engage in regular vigorous endurance exercise training was approximately one-half the rate of decline seen in age-matched sedentary subjects. Also the rate of decline in maximal heart rate was decreased (197).

Other age-related cardiovascular changes include reduced blood flow capacity to peripheral tissue, narrowing of coronary artery and decreased blood vessel compliance (40, 198). The incidence of cardiovascular diseases (CVD) increases linearly with age. More than 70% of males and females over 75 years of age present some clinically evident CVD (199). Blood pressure increases with age and it is associated with structural changes in the arteries and especially with large artery stiffness that is mainly due to arteriosclerotic structural alterations and calcification. This leads to an increase in systolic blood pressure. Diastolic blood pressure tends to increase up to the age of about 50 due to an increase in arteriolar resistance, after which it ted to plateau or even decrease. This leads to an increase in mean arterial pressure, increase in pulse pressure and aging is also associated with decreased ability to respond to abrupt hemodynamic changes (200). Increased blood pressure raises the risk of heart disease, stroke, and kidney disease. Nowadays it has been recognized that age-related blood pressure changes are multifactorial in aetiology and lifestyle and environmental factors, such as psychological stress,

sodium intake, obesity, sedentary lifestyle and low birth weight, are the most important determinants of age-related blood pressure changes (201).

2.3 DEVELOPMENTAL PROGRAMMING

According to the DOHaD-hypothesis several metabolic and other non-communicable disorders have their origins in prenatal life and childhood (16). This phenomenon has been called fetal programming. Programming refers to the process of sustaining or affecting a stimulus or impairment that occurs at a crucial point during development (202). Non-optimal growth during prenatal life, indicated by e.g. low birth-weight, can have long-term health consequences later in life. Low birth weight has been associated with all-cause mortality, an increased risk of developing type 2 diabetes and coronary heart disease later in life (18, 203, 204). Low birth weight has also been linked with altered skeletal muscle fiber composition, decreased muscle strength in adult life, lower physical functioning at older age and lower leisure time physical activity (20, 205-207). Also, certain maternal traits, like maternal adiposity, excessive gestational weight gain, dietary patterns in pregnancy and low vitamin D status, have been associated with childhood adiposity (208-211). In addition to reducing later functional capacity, small body size at birth also modifies later responses to childhood and adult environment. For example, an increased risk of coronary heart disease and type 2 diabetes is associated with slow growth in utero, coupled with accelerated weight gain during childhood (204, 212). Also, children who were born short and then gained height poorly during childhood have been found to have an increased risk of hip fracture (213).

Prenatal developmental adaptations play important roles for example in the human propensity to deposit fat. Godfrey et al (214) has shown that across the range of fetal size and independent of the mother's adiposity and parity, greater liver blood flow was associated with greater offspring fat mass as measured by DXA, both in the infant at birth and at age 4 years. In contrast, smaller placentas that are less able to meet fetal demand for essential nutrients were associated with a brain-sparing flow pattern. The authors propose that

humans have evolved a developmental strategy to prioritise nutrient allocation for prenatal fat deposition when the supply of conditionally essential nutrients requiring hepatic inter-conversion is limited, switching resource allocation to favour the brain if the supply of essential nutrients is limited. In circumstances of maternal adiposity and nutrient excess these processes can also lead to prenatal fat deposition.

Genetic variation can moderate the relationship between prenatal environmental factors and epigenetic status at birth. Although the effect of fixed genetic variation on DNA methylation is apparent in studies of allele-specific methylation and genomic imprinting, there is also emerging evidence for environmental influences as a source of epigenomic variation. It has been shown that genetic differences alone best explained 25% of the epigenetic variation between neonates, with the remaining 75% been explained by the interaction of genetic differences and the prenatal environment (215). The authors found that the best explanation for 75% of variably methylated regions of neonates was the interaction of genotype with difference in utero environments, including maternal smoking, maternal depression, maternal BMI, infant birth weight, gestational age, and birth order (215). There is also growing evidence that epigenetic mechanisms (DNA methylation, histone modification and non-coding RNAs) are responsible for tissue-specific gene expression during growth and development and that these mechanisms underlie the processes of developmental plasticity (216). When the phenotype is mismatched to the later environment or from rapid environmental change, risk of non-communicable diseases (NCDs) increases (216).

Both parents contribute to offspring genetics. Unique maternal factors include altered structure/function of reproductive organs, alterations in vaginal or gut microbiome, mitochondrial DNA inheritance, placental function, or epigenetic phenotypes in female germ cells (217). Unique paternally-mediated effects on offspring implicate indirect effects on the fetal component of the placenta, seminal fluid proteins, or sperm epigenetic mechanisms (217).

2.4 PHYSICAL FITNESS, FUNCTIONING AND PERFORMANCE

2.4.1 DEFINITION

Physical fitness is a state of health and well-being and expresses the ability to perform muscular work satisfactorily including aspects of sports, occupations and daily activities. Being physically fit has been defined as the ability to carry out daily tasks with vigour and alertness, without undue fatigue and with ample energy to enjoy leisure pursuits and to meet unforeseen emergencies (1). Physical fitness is a set of attributes that people have to achieve that relates to the ability to perform physical activity. Physical fitness can be divided to health-related fitness that pertains physical well-being and to skills related, or motor or performance-related fitness, that pertains athletic ability (37). Performance-related fitness refers to those components of fitness that are necessary for work or sport performance and depends on motor skills, cardiorespiratory capacity, muscular strength, body composition and nutritional status (218). Health-related fitness refers to those of fitness that are affected by habitual physical activity and relate to health status (218). The components of health-related physical fitness are suggested to be cardiorespiratory endurance, muscular strength, muscular endurance, body composition and flexibility (37).

Pate has proposed a newer approach to define physical fitness and according to him physical fitness is a state characterized by (a) an ability to perform daily activities with vigour, and (b) demonstration of traits and capacities that are associated with low risk of premature development of the hypokinetic diseases (i.e., those associated with physical inactivity) (219). According to him fitness components encompassed by this definition are cardiorespiratory endurance, body composition, muscular strength and endurance, and flexibility and the status on each component can be improved through exercise training and each can be associated with important health outcomes (219).

According to Pate motor performance is a broader concept than physical fitness and might be defined as the ability to perform physical skills and

vigorous physical activities including those involved in sports and athletics (219). Motor performance includes in addition to the above-mentioned components also aerobic power, speed, flexibility and agility.

Physical functioning is defined as the ability to perform activities that require physical actions such us activities of daily living to more complex activities that are not required for independence but have an impact on quality of life (220). It is needed to be able to successfully perform everyday activities such as personal care, housework and shopping. Physical functioning is a multidimensional concept, with four related subdomains: mobility (lower extremity function), dexterity (upper extremity function), axial ability (neck and back function), and ability to carry out instrumental activities of daily living (221). It is influenced by a combination of physiological, psychological, and socio-cultural factors. Physical functioning is usually measured objectively with physical performance tests.

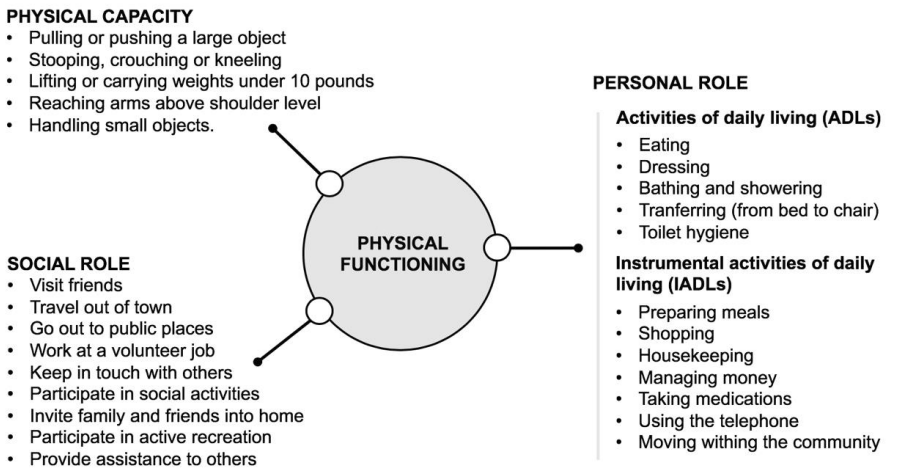

Figure 3 Physical functioning in aging adults. (Modified from The Epidemiology of Aging)(3).

2.4.2 MEASUREMENT METHODS

Attributes of physical fitness can not be directly measured. The most frequently measured components of physical fitness fall into two groups: one related to health and the other to skills that are related to athletic ability (222). Health-related physical fitness includes cardiorespiratory endurance, body

composition, muscular strength and flexibility. Athletic performance related physical fitness includes components such as isometric strength, power, speed–agility, balance and arm–eye co-ordination. Tests can be divided to field and laboratory tests.

When assessing physical functioning among older people there are three relevant domains; personal roles, social roles and physical capacity (Figure 3). Personal roles include self-care tasks known as activities of daily living (ADLs) and include functions such as eating, dressing, bathing, transferring from bed to chair and using the toilet (3). Personal roles also include tasks needed for independent living in community and are referred as instrumental activities of daily living (IADLs) and include preparing meals, shopping, housekeeping, managing money, taking medications and using the telephone (3). Social role functions include such items as visit friends, go to public places and participate in social activities which are important for satisfying life (3). Physical capacity includes functional capacity and mobility and includes activities such as lifting and carrying things, pulling things, climbing stairs, walking, running and can be self-reported or measured with physical performance tests. The health components of functioning and disability can be classified by The International Classification of Functioning, Disability and Health (ICF) (223). The classification covers three dimensions; body functions and structure, activities related to tasks and actions by an individual and participation in a life situation and additional information on severity and environmental factors. It allows to assess the degree of disability, although it is not a measurement instrument and it can be used at both individual and population level.

Physical performance can be measured by self-reported questionnaires, performance measures of specific task or laboratory tests. There are several questionnaires that assess functional status. These self-report instruments usually ask people whether they are capable of performing a task or whether they actually perform the task. The limitations of physical functioning can be qualified and quantified be these tests. Normative scale values can be available for the specific population to help to determine variations in health status and assess the effectiveness of interventions. One example of a self-administered

functional assessment is the Physical Functioning Scale of the 36-Item Short Form Health Survey (SF-36), that has also been validated in older adults (224). Laboratory tests include traditional incremental exercise tests on treadmill or cycloergometer. The peak oxygen uptake is the gold standard in the assessment of exercise tolerance (225) and gives information on individuals maximal exercise capacity and can to some extent reflect capability to manage tasks of daily living (226). These tests require however expensive equipment and are not feasible for large populations. Also the maximal exercise tests can be unsafe and inappropriate for testing older people (227).

Physical performance tests can measure only one physical capability, such as grip strength (228, 229), walking speed (230-232), chair rising (233) or standing balance (234) or be a battery of such tasks. A typical outcome measure is the time to perform a standardized task. Physical performance is often an outcome variable in clinical studies, and it helps to evaluate aspects of health and disability. A review (235) has obtained predictive validity of physical performance tests regarding mortality, dependence, difficulty, falls, global health improvements and difficulty in walking and upper extremity performance.

Initially most physical performance tools detected functional limitations at the behavioural level, for example assessed individuals' capability to perform specific daily-living activities such as bathing, dressing and walking. One of these tests is the Physical Performance Test (PPT) that includes writing a sentence, simulated eating, turning 360 degrees, putting on and removing a jacket, lifting a book and putting it on a shelf, picking up a penny from the floor, a 50-foot walk test, and climbing stairs (scored as two items) (236). The Performance Test of Activities of Daily Living (PADL) measures a variety of tasks that are required in daily living (237). With these instruments the functional limitation may be detected before it becomes measurable by traditional self-reported questionnaires (238, 239).

A study has shown at both population and individual level, that handgrip strength and knee extension strength was only low to moderately correlated and was independent of age and health status (240). Therefore, handgrip strength alone should not be assumed a proxy for overall muscle strength.

Nowadays physical performance is actually often assessed by tests that identify different dimensions (e.g., strength, mobility, dexterity) of physical functioning that are essential for meeting activities of daily living. Some of the tests batteries evaluate only the lower extremity functioning such as The Short Physical Performance Battery (SPPB) that includes gait speed, chair stand and balance tests (241). One test battery that has been developed especially for older adults and is based on a functional fitness framework is the Senior Fitness Test (SFT) (242). It is based on the fact that being able to perform everyday activities (e.g. personal care, shopping, housework) requires the ability to perform functional movements, such as walking, stair climbing and standing up; and that these functional movements, in turn, are dependent on having sufficient physiologic reserve (i.e. strength, endurance, flexibility, balance). The Senior Fitness Test measures physiologic parameters using functional movement tasks, such as standing, bending, lifting, reaching and walking (243).

2.4.3 PHYSICAL PERFORMANCE AND AGING

Good physical fitness is related to many health benefits. Poor physical fitness is associated with cardiovascular mortality (244) and overall mortality (245, 246) and good physical fitness has an protective effect of many non-communicable diseases (247-249). Age-associated deterioration in physical performance can be attributed to both primary aging processes and to life-style factors. VO_{2max} declines at a rate of 1% per year after the third decade of life (250) and the decreased cardiorespiratory function and muscular performance associated with advancing age and inactivity can significantly diminish an individual's functional capacity (251). Many sedentary older adults are very close to the aerobic capacity threshold and any further decline results in them being unable to perform their activities of daily living and thus impair their ability to live independently. The greater the maximal performance in physiological components such as muscle strength, power and endurance, the greater is the reserve capacity for the physical performance of activities of daily living and the potential for the continuation of independent life in older adults. A cut point between low physical function (requiring

assistance with activities of daily living) and high physical function (independent living) has been proposed to be 18.3 ml/kg per min (226). Another study has reported the minimum level of VO_{2max} that corresponds to a fully independent life at age 85 in to be 17.7 ml/kg per min for men and 15.4 ml/kg per min for women equivalent to 5,1 and 4,4 MET respectively (252).

The morphologic components of fitness (i.e. body composition, bone density and flexibility) are associated to functional limitations (253). Body mass index, reduced bone density and decreased range of motion has all been related to decreased functional disability (254-256). Muscle mass and strength decreases with age. Reduced muscle strength has shown to be associated with risk of falls (257), reduced gait speed (258) and loss of balance (259) and increased disability (260). Morey el al (253) have shown all three fitness components (cardiorespiratory, morphologic, and strength) to be associated with functional limitations in older adults after controlling for age, race, sex, education, depressive symptoms, and body mass index.

2.4.4 PHYSICAL ACTIVITY AND PHYSICAL PERFORMANCE IN OLD AGE

Decline in physical performance in old age is associated with loss of independence, institutionalization and mortality (261-263). Regular aerobic and strength exercise participation is an effective way to reduce a number of functional declines associated with aging (264). Regular endurance training helps to maintain and improve cardiovascular function and to enhance submaximal performance (265, 266). Physical activity is associated with reductions with many age-related diseases, for example coronary heart disease, diabetes, cancer and also associated with increased life expectancy (7). Strength training diminishes the loss of muscle mass and strength associated with aging (267). Regular exercise also improves bone health and, thus, reduces the risk of osteoporosis, improves postural stability and thereby reduces the risk of falling and associated injuries and fractures (268, 269). Exercise also increases flexibility and range of motion (270). Physical activity has also been associated with number of psychological benefits, such as the preservation of cognitive function, reduction in depression, and an

improvement in self-esteem and self-efficacy (271-273). Participation in physical activity might improve health and functional capacity of older adults even if it may not increase the traditional markers of physiological performance and fitness (e.g. VO_{2max}) (274). On the other hand, a review has shown that there is a dose-response relationship between both physical activity and cardiorespiratory fitness and health outcomes (reduces morbidity from coronary heart disease, stroke, CVD and cancer; and mortality of CVD, cancer and all-cause mortality), but the dose-response gradient is steeper for cardiorespiratory fitness than physical activity (275).

A study that explored the genes associated with aging found mitochondrial dysfunction to be the major age-related factor mitochondrial genes showing decreased expression with aging (276). They also found that 21 of the 957 genes associated with aging were also associated with VO2max and that 20 of these genes are regulated in opposite direction when comparing increasing age with increasing VO2max (276). Their findings support the importance of preserving high physical fitness during old age to counteract negative effects on mitochondrial function.

2.5 HEALTH-RELATED QUALITY OF LIFE

2.5.1 DEFINITION

Quality of life is a concept that broadly covers all aspects of human experience of the necessities of life. HRQoL reflects how the individual perceive and react to their health status and also to element not related to health. It is a multidimensional concept that incorporates physical, mental, emotional and social aspects. It is a subjective measure of the individual's wellbeing, how they experience diseases or symptoms and limitations caused by illnesses (277). According to WHO HRQoL does not merely mean the absence of a disease, but is a state of complete physical, mental and social well-being (278). It is a double-sided concept, incorporating positive as well as negative aspects of well-being and life, and it is multidimensional, incorporating social, psychological and physical health. It is also a dynamic concept resulting from past experience, present circumstances, and expectations for the future and

has both positive and negative aspects (279). In the field of HRQoL research, two major domains of HRQoL is usually recognized; functioning including physical, cognitive and social functioning and subjective well-being including perception of health, emotional functioning and self-concept (280).

2.5.2 ASSESSMENT OF HEALTH-RELATED QUALITY OF LIFE

As HRQoL is an important indicator of an individual's physical, mental and overall health, assessing HRQoL is an essential component in healthcare evaluation instead of only measuring the frequency and severity of diseases. Both the life expectancy and the expectations of morbidity-free life in old age has increased and enhanced the need to measure HRQoL. Also, the healthcare providers want to evaluate the effects of treatments and health interventions and the policymakers want to know the cost-effectiveness of healthcare. The ultimate criterion on the quality of health care is how the patient is feeling after a treatment (281).

The physical, mental and social aspects of HRQoL can all be either subjectively or objectively measured. Objective measurement encompasses only individual's behaviour or level of functioning (282). These quality of life instruments measure objectively the adequacy of individuals' functioning across physical, occupational, and interpersonal domains (283). Subjective and objective data can also be combined to give a profile of HRQoL status. Because HRQoL is a subjective experience how individual perceive his/her well-being, it is most often self-reported. However, sometimes objective assessment is needed because of the physical condition or age of the patient.

HRQoL can be measured either by unidimensional or multidimensional assessment. In unidimensional measurement a single global question is used to assess the overall HRQoL status. Because HRQoL is a multidimensional concept, the multidimensional approach is widely used (284). In multidimensional approach HRQoL instruments measures a broad perception (symptoms, functioning, disability) of physical, mental and social health and the extent of difficulties with activities of daily living and how these difficulties affect relationships with family, friends, and social groups. Often a global score is composed from the different components of HRQoL assessment.

HRQoL status can be measured on a generic basis or a disease-specific basis (285). When HRQoL is measured on a generic basis the dimensions of physical health, mental health, social functioning, role functioning and general well-being should be encompassed (286). A generic scale enables to compare different kind of diseases, conditions and treatments. Disease-specific scale assesses only a disease- or condition-related attribute and it is used when comparing health status and responsiveness across diseases or conditions. The instrument used to measure the health state can be specific to the disease, population, function or problem. A HRQoL instrument can give one score and/or a profile (281). An advantage of a single score instrument is that the quality of life and the change in it can be shown with one number. Anyway, it does not tell from which factors the quality of life consists in contrast to profile instruments.

One of the disease-specific instruments designed for a specific patient population is the PAS (Pasieka's Assessment Score). It is a patient-based surgical outcome questionnaire that can be used to assess the severity of symptoms on a visual analogue following parathyroidectomy in patients with primary hyperparathyroidism (287). It has been shown to be correlated with a generic tool measuring HRQoL, the SF-36 questionnaire (288). Another example is an instrument to measure HRQoL is the QOLAURTI questionnaire that measures the HRQoL related to upper respiratory tract infections (289).

The Finnish 15D is a generic, comprehensive, 15-dimensional, standardized and self-administered measure of HRQoL (290). It can be used both as a single index score measure and as a profile of 15 different dimensions (mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity) presented as a graph (290). Each dimension comprises one question with five options. The 15D instrument has good test–retest reliability, construct validity, and discriminatory power in general populations (290). It is sensitive reacting to treatment related change (291).

SF-36 is also a generic health survey (292, 293). The SF-36 is a questionnaire with 36 items which taps eight multi-item variables: physical functioning, bodily pain, role limitations due to physical health problems, role

limitations due to personal or emotional problems, general mental health, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health. The interpretation of SF-36 can be grouped into three main categories: 1. content-based interpretation; 2. construct-based interpretation; and 3. criterion-based interpretation (294). Content-based interpretation uses information about item content and patterns of response choices to assign meaning to scores (295). A score for all dimensions can be given. Constructs are abstract properties, such as physical or mental health, which can be measured with SF-36. Construct-based interpretation answers questions about the underlying meaning of health concepts, such as "where does a scale fit into a general model of health"? One way to determine this is to examine the relationship among scales within a questionnaire. SF-36 can be divided to physical and mental functioning scale (296). Criterion-based interpretation uses information on the relationship of scores to external variables to determine their meaning. Scores can be interpreted in relation to clinically and socially meaningful variables, such as job loss, utilization of health care services, likelihood of a clinical diagnosis, or death. SF-36 scores can be interpreted in relation to normative data. The SF- 36 can be scored so that all scales and summary measures are on the same metric, where 50 is the mean for the US general population and 10 is the standard deviation (297). This scoring advance makes it easier to compare scale scores, which have different average values and standard deviations on the traditional 0-100 metric.

2.5.3 SUCCESSFUL AGING AND HEALTHY AGING

Rowe and Kahn defined successful aging as having no disease in 1987 (298). In 1998, Rowe and Kahn expanded their definition to include three criteria: (a) absence of disease, disability, and risk factors like high blood pressure, smoking, or obesity; (b) maintaining physical and mental functioning; and (c) active engagement with life (299). This last criterion included both being connected to other persons and engaging in productive activities. To be aging successfully one had to meet all three criteria, making it likely that successful aging would still describe only a relatively small proportion of older persons

and exclude those with chronic conditions. According to Rowe and Kahn successful aging implies aging that is better than "usual aging". The definition of successful aging of Rowe and Kahn has been modified by researchers defining successful aging as having minimal disease and disabilities and exhibiting high levels of physical functioning (300). However, the majority of researchers regard successful aging as minimal interruption of usual function, although minimal signs and symptoms of chronic disease may be present. Successful aging can also be described as doing the best with what one has (301). Successful aging refers to the capacity to function across many domains and is proposed to have three dimensions corresponding to cognitive, social and emotional perspectives and is in large part what older adults value in the quality of their life and their death (302).

A review of 28 studies of adults over age 60 found the most frequent significant correlates of successful aging to be age, non-smoking, and absence of disability, arthritis, and diabetes (303). Moderate support was found for greater physical activity, more social contacts, better self-rated health, absence of depression and cognitive impairment, and fewer medical conditions (303). Gender, income, education, and marital status generally did not relate to successful aging (303).

Healthy aging refers to the physical and cognitive functional preservation, but without the requirement of disease avoidance (304). WHO defines healthy aging "as the process of developing and maintaining the functional ability that enables wellbeing in old age" (305). Functional capacity refers to the individual's ability to meet basic needs, learn, grow and make decisions, be mobile, build and maintain relationships and contribute to society. Functional capacity is made up of individual's intrinsic capacity and environmental characteristics and of their interaction. Intrinsic capability includes individual's mental and physical capacities and ability to walk, think, see, hear and remember. Intrinsic capacity is affected by many factors such as genetics, presence of disease, injuries and age-related changes. Built environment, people and their relationship, attitudes and values, and health and social politics comprises the environmental surrounding that affect older people's life. According to WHO healthy aging requires a change in the way we think

about aging and older people, creation of age-friendly environments, alignment of health systems to the needs of older people and development of systems for long-term care (305).

2.5.4 HEALTH-RELATED QUALITY OF LIFE, PHYSICAL ACTIVITY AND AGING

Quality of life is an important concept to consider in relation to successful aging. Quality of life is indicative of poor or successful aging processes (306). At advanced age, poor HRQoL have been related with such sociodemographic factors as being older, female, poorly educated and belonging to low social class (307). Also, the presence of mobility problems, pain/discomfort and anxiety and depression have been shown to be highly correlated with the HRQoL of the elderly while problems of self-care and with usual activities have a weaker association (307).

Physical activity has been shown to be associated with better HRQoL among children and adolescence (308), in the general adult population (309) and also among community dwelling elderly (310). A cross-sectional study has shown that physical activity and quality of life were both in part significantly associated with successful aging among adults aged 65 years or older (311). Older adults who participate more in physical activity consider themselves to have aged more successfully (311). Menai et al (312) have shown that participants undertaking ≥150 minutes of MVPA per week were more likely to be successful agers with both self-reported and accelerometer measured PA. In the study, successful aging was defined as good cognitive, motor, and respiratory functioning, along with absence of disability, mental health problems, and major chronic diseases. Also a study done among older men has shown that sustained physical activity was associated with improved survival and healthy aging (313). In this study, also vigorous physical activity was found to be associated with successful aging. A study done among older adults has also shown that both self-reported MVPA and daily steps measured with a pedometer were associated with HRQoL (314). Participants in the high-step group (>10,000 steps/day) had significantly higher scores on mental health, physical health and global health than participants in the low-step group (0-

6,999 steps/day). The participants were also divided into groups according to not meeting MVPA guidelines (<150 min of MVPA per week), meeting MVPA guidelines (150-299.9 min of MVPA per week), or exceeding guidelines for additional health benefits (≥300 min of MVPA per week). Participants who met or exceeded the MVPA guidelines had significantly higher scores in mental, physical and general health compared to the participants in the inactive (not meeting MVPA guidelines) group (314). Researchers reported no differences between the MVPA and pedometer step models on mental, physical and general quality of life indices. The current recommendation of WHO for older adults of PA level is at least 150 minutes of moderate-intensity aerobic PA throughout the week or do at least 75 minutes of vigorous-intensity aerobic PA throughout the week or an equivalent combination of moderate- and vigorous-intensity activity (6). It have been suggested that the range for healthy older adults is 7,000 and 10,000 steps/day, which is estimated to be equivalent to the recommended 150 min of MVPA per week (315). A recent prospective study done among older women has actually shown that reaching the often-repeated goal of 10 000 steps per day may not be necessary. In a cohort of 16 741 women with a mean age of 72 years, women with averaged 4400 steps/d had significantly lower mortality rates during a follow-up of 4.3 years compared with 2700 steps/d (316). With more steps per day mortality rates progressively decreased before levelling at 7500 steps/d (316).

There are also many exercise interventions showing the impact of PA on HRQoL. Pedersen et al (317) divided participants of an average age of 80 years to team training, resistance training and a control group. Training groups trained for 1 hour twice a week for 12 weeks. Both team and resistance training led to significantly higher scores in the subscales of psychological well-being, general quality of life, and health-related quality of life, as well as decreased anxiety and depression levels. The same effect has been shown with participating in dance sport or multicomponent training program (318).

There are many studies that have explored the association between physical activity, sedentary behaviour and HRQoL in older populations. Vagetti et al (277) evaluated in a systematic review the association of physical activity with specific domains of HRQoL in the elderly in the literature published between

2000 and 2012. In their review of 42 studies (eleven intervention and 31 observational studies) they divided quality of life into 16 subdomains and determined the consistency of the association between physical activity and the subdomains of quality of life. They found a consistent and positive association between a physical activity and the functional capacity, general quality of life, autonomy, past, present, and future activities, death and dying, intimacy, mental health, vitality and psychological domains (277). A moderate association was shown to be between physical activity and physical, emotional, overall health, social relations, pain and environment domains of quality of life (277). The results showed an inconsistent association between physical activity and the sensory ability domain (277).

There are also studies that have examined the dose-response relationship between physical activity and HRQoL in older adults. Ku et al (319) found in their study that MVPA and light physical activity at baseline assessed by using triaxial accelerometry were associated with different dimensions of well-being and sedentary time was not related to any dimension of well-being 18-month months later.

Table 1 The effect of physical activity on health-related quality of life (HRQoL) in old age.

Study	n=	Age	Setting	Physical Activity	QoL	Major findings
Intervention studies						
Ballin (2019)(320)	77	70 (m+w)	RCT	10 wk progressive interval training	SF-36	MCS↑, PCS-
Battaglia (2016)(321)	30	69 average (w)	RCT	8 wk PA intervention program, 2x/wk	SF-36	MCS↑, PCS↑ in training group
Broekhuizen (2016)(322)	235	60-70 (m+w)	RCT	Internet-Based PA intervention. Triaxial accelerometer measured PA baseline and after 3 months.	RAND-36	Emotional and mental health, and health change↑, Total HRQoL-
Gusi (2015)(323)	3214	>50 (m+w)	CT	1 yr participation in PA program, exercise 50-60 min 3x/wk	EQ-5D	HRQoL ↑ or -
Haraldstad (2017)(324)	49	60-81 (m)	Intervention	12 wk strength training	SF-12	Positive correlation between improvements in muscle strength and better physical and social function
Lok (2017)(325)	80	>65 in nursing home (m+w)	RCT	10 wk PA program, 60 min 4 x/wk	SF-36, BDI	Physical Health, Physical Role, Pain, General Health Perception, Vitality , Social Function, Emotional Role and Mental Health subdimension all ↑,BDI↓
Martín-Valero (2013)(326)	100	59-69(m+w)	RCT	3 months PA promotion program, 60 min 2xwk/health education	EQ-5D	HRQoL in men↑, in women -
Pietta-Dias (2019)(327)	48	>60 (w)	CT	12 wk strength/endurance/combine training 2x/wk / control	SF-36	Strength MH↑, PH↑, endurance MH↑, PH-, combined MH↑, PH↑, control MH-, PH-
Pedersen (2017)(317)	72	67-93 (m+w)	RCT	12 wk/ team sport/ resistance training, 60 min 2x/wk	SF-12	Both resistance and team training, HRQoL ↑ and depression ↓
Taguchi (2010)(328)	65	74-96 (m+w)	CT	12 months multicomponent exercise program	PGC-morale scale, GDS, TMIG-IC	No difference in HRQoL between intervention and control group

Vreede (2007)(329)	98	>70 (w)	RCT	12 wk functional task/resistance exercise program 3x/wk/control	SF-36	Only in functional group functioning score increased, but only at 3 months (not at 6 or 9 months)
Prospective and cross-sectional studies						
Acree (2006)(330)	112	<70 (m+w)	Cross-sectional	Johnson Space Center physical activity scale	SF-36	All 8 domains higher in more active group
Balboa-Castillo (2011)(331)	1097	>62 (m+w)	Prospective (6 yr)	LTPA questionnaire	SF-36	Greater LTPA and less LTSB were independently associated with better long-term HRQoL (physical functioning, physical role, bodily pain, vitality, social functioning, emotional role, mental health)(all other than general health)
Bertheussen (2011)(332)	4500	19-91 (m+w)	Cross-sectional	PA questionnaire	SF-8	PCS↑, MCS↑, >65 years association was stronger
Buman (2010)(333)	862	>65 (m+w)	Longitudinal (2 yr)	Accelerometry measured PA	Self-reported	Light PA associated with physical health and well-being
Choi (2013)(334)	1926	60-79 (w)	Prospective (7 yr)	Change in self-completed questionnaire measured MVPA	Change in EQ-5D	Positive change in MPVA was associated with improved or maintain in HRQoL
Halaweh (2015)(310)	176	>65 (m+w)	Cross-sectional	PA-SCAQ (questionnaire)	EQ-5D	Strong association between higher levels of PA and all dimensions of HRQoL
Heesch (2012)(335)	18344	50-80 (w)	Concurrent and prospective	Total weekly PA (walking+ MVPA)(questionnaire)	SF-36	Both concurrent and prospective walking and TPA associated with better HRQoL
Heesch (2016)(336)	555	81-84 (w) with a history of depressive symptoms	Cross-sectional and prospective	Active Australia survey	SF-36	PCS↑, MCS↑

Kell (2019)(337)	46 564	>65 (m+w)	Prospective (7 yr)	Participation in exercise program	SF-12, self-rated health, BRFSS health days	PCS↑, MCS↑, Self-rated health↑, Unhealthy days↓
Koolhaas (2018)(338)	5 554	Mean 69 (m+w)	Cross-sectional	LASA Physical Activity Questionnaire (LAPAQ)	EQ-5D	HRQoL↑
Lee (2003)(339)	10063	70-75 (w)	Cross-sectional	Self-reported PA	SF-36 (MCS and mental health subscales)	PA associated with MCS and mental health subscales
Lee (2003)(339)	1999	73-78 (w)	Longitudinal (3 yr)	Self-reported PA	SF-36 (MCS and mental health subscales)	PA associated with better MCS and mental health subscales, but weaker that cross-sectional
Salguero (2011)(340)	436	60-98 (m+w)	Cross-sectional	YPAS	SF-36	PC correlated with PA, but MC not
Vallance (2010)(341)	297	Mean 61 (w)	Cross-sectional	Self-reported meeting PA guidelines	RAND-12, GDS	PCS↑, MCS↑, PA was associated with lower depression symptoms
Vallance (2012)(342)	387	>55 (m)	Cross-sectional	Questionnaire, achieving versus not achieving PA recommendations	RAND-12	PHC↑, MHC↑, Global score↑
Vallance (2016)(314)	1296	>55 (m+w)	Cross-sectional	Pedometer measured steps/day and self-reported MVPA	RAND-12	Higher amount of step and MPVA was associated with PCS↑, MCS↑, GHS↑
Wanderley (2011)(343)	85	60-83 (m+w)	Cross-sectional	Accelerometer measured PA	SF-36	PA associated with higher on physical functioning subscale and role limitations due to physical problems, not bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, mental health

Depressive symptoms						
Gouveia (2017)(344)	802	60-79 (m+w)	Cross-sectional	Baecke questionnaire	SF-36	PA was associated with total score of SF-36
Jung (2017)(345)	3191	70-95 (m+w)	Cross-sectional	Accelerometer measured PA	Geriatric Depression Scale-15	Step count and MVPA not differed between participants with or no depressive symptoms, Participants with no depressive symptoms had higher LPA
Ku (2017)(9)	274	>65 (m+w)	Prospective (2 yr)	Triaxial accelerometer measured PA	Geriatric Depression scale-15	MPVA, LPA associated with less depression symptoms, sedentary time with increased risk of depression symptoms
Reviews						
Rejeski (2001)(346)	12 articles	>60 (one article 51-53) (m+w)	RCT, 1 quasi-experimental, 5 cross-sectional	PA	QoL	RCT: conflicting results, cross-sectional: PA associated with QoL
Svantesson (2015)(22)	30 articles	>65 (m+w)		PA, physical performance	Quality of life, cognition	PA and physical performance were associated with QoL and prevents cognitive decline
Vagetti (2014)(277)	42 articles (2000-2012)	>60 (m+w)	Cross-sectional, longitudinal, intervention	PA	Quality of life	A consistent and positive association between PA and the functional capacity, general QoL, autonomy, past, present, and future activities , death and dying, intimacy, mental health, vitality and psychological domains. A moderate association between PA and the following domains: physical, social relations, emotional, overall health, pain, and environment. The results showed an inconsistent association between PA and the sensory ability domain.

Abbreviations: QoL, quality of life; m, men; w, women; RCT, randomized control trial; wk, week; SF-36, short form 36; MCS, mental component scale; PSC physical component scale; PA, physical activity; RAND-36, RAND 36-item health survey; HRQoL, health-related quality of life; CT, control trail; yr, year; EQ-5D, EuroQol-5-dimensions; SF-12, short form 12; BDI, Beck's Depression Inventory; MH, mental health; PH, physical health; PGC-morale scale, Philadelphia Geriatric Center morale scale; GDS, geriatric depression scale; TMIG-IC, The Tokyo Metropolitan Institute of Gerontology Index of Competence; LTPA, leisure-time physical activity; LTSB, leisure-time sedentary behaviour; SF-8, short form 8; MVPA, moderate to vigorous physical activity; PA-SCAQ, physical activity-socio-cultural adapted questionnaire; TPA, total physical activity; BRFSS, Behavioural Risk Factor Surveillance System; YPAS, Yale Physical Activity Survey; PC, physical component; MC, mental component; RAND-12, RAND 12-item health survey; GHS, global health status; LPA, light physical activity.

2.6 TELOMERES

2.6.1 STRUCTURE AND FUNCTION

Telomeres are chromatin structures at the ends of eukaryotic chromosomes, which consist of tandem DNA repeats (of TTAGGG) and associated proteins (24) (Figure 4). They stabilize chromosomes. Broken ends of chromosomes lacking telomeres are unstable and subject to recombination, often leading to fusion with other broken ends or terminal degradation leading to loss of internal sequences (347). The other important function of telomeres are that they allows the end of chromosomal DNA to be replicated completely without loss of terminal at the 5' end of the chromosomal DNA (24). Such loss is predicted from the replication as the replication machinery can work only in 5' to 3' direction and the DNA polymerase needs an RNA primer. Telomeres shorten every time the cell replicates and eventually become critically short, causing cells to become senescent or die.

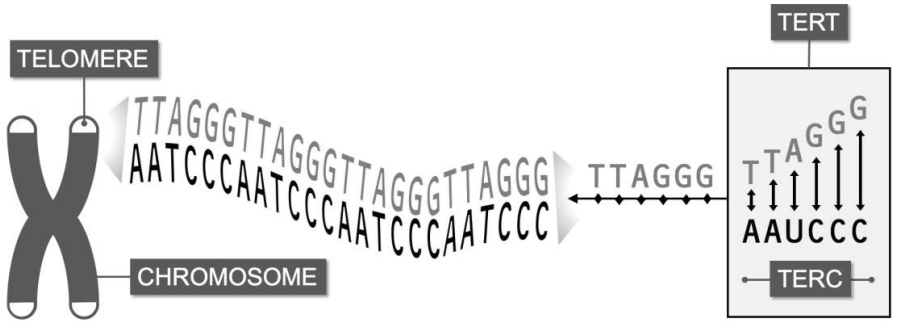

Figure 4 Telomere structure. Tert = telomerase reverse transcriptase, Terc=telomerase RNA component.

Telomerase is an enzyme, a reverse transcriptase, that is responsible for synthesis of the telomeric DNA (348). The action of telomerase explains how replication of the 5' ends of the chromosomal DNA can be completed without the loss of terminal sequences since the continuous addition of telomeric DNA to the chromosomal ends by telomerase will counterbalance the terminal DNA

attrition (348). Most somatic tissues lack telomerase activity and show progressive telomere shortening coupled to cell division. Cells requiring high replicative capacity, such as stem cells, express telomerase (349). Also, most of cancer cells has activated telomerase (350).

Telomeres end in a single-stranded nucleotide overhang. The telomerase reverse transcriptase (Tert) recognizes the 3'-OH group at the end of this overhang. The telomerase elongates telomeres from this group using an RNA molecule, the Terc (telomerase RNA component) as a template (351). The proteins associated with telomeres include telomere repeat binding factors 1 and 2 (T(E)RF1 and T(E)RF2) which can directly bind to the TTAGGG repeats and can also act with other factors, forming large protein complexes. TERF1 protein complexes control telomere length by regulating the access of telomerase to the telomere (352). The role of TERF2 complex is to protect telomeric single-stranded overhang from degradation and from DNA repair activities, thereby preventing telomere end-to end fusion (352).

2.6.2 TELOMERES AND AGING

Telomeres are proposed to be a marker of aging, but it does not fulfil all the criterion of a biomarker of aging stipulated by the American Federation of Aging Research (353). The association between telomere length and mortality is still contradictory, and telomere length is not a better predictor of life span than chronological age (25). There is an inverse association between chronological age and telomere length. There is clear evidence that telomeres are involved in cellular aging and human disease of premature aging, but whether telomere length is correlated with measures of normal aging is still unclear and the second criterion that the biomarker of aging must monitor the basic process that underlines the aging process, not the effect of disease does not completely fulfilled (25). Telomere length fulfils the third and fourth criterion, that telomere length estimation can be taken repeatedly with minimal harm and telomere length can be examined in other mammals.

2.6.3 METHODS OF MEASUREMENT

The two main methods measuring telomere length are the more traditional telomere restriction fragment method (TRF) and a quantitative real-time PCR technique.

In the TRF method genomic DNA is enzymatically digested and intact telomeres from all chromosomes are resolved based on size using agarose gel electrophoresis and telomeric fragments are visualized by either southern blotting or in-gel hybridisation using a telomeric DNA specific probe (27, 354). With the TRF method it is possible to provide a kilobase size estimate for telomere length and to compare results to those obtained by other investigators. But the TRF method requires large amounts of DNA and time and accurate determinations are not possible when DNA is broken. Furthermore, the relative mean TRF lengths of individuals can vary by as much as 5 % depending on the particular restriction enzymes used (355, 356). Also, subtelomeric DNA is included in the analyses, because of the restriction enzymes used, and this leads to overestimation of the true telomere length.

With PCR the DNA sequence of interest is amplified using specific primers and the PCR product is quantified with use of fluorophore. Telomere length is quantified by comparing the telomere amplification product (T) to that of a single-copy gene (S). The T/S ratio is then calculated to yield a value that correlates with the average telomere length, but is not a base pair estimate (355). It does give a mean length measure but does not recognize individual short telomeres or ends lacking telomeres (357). The quantitative PCR method can use small amounts of DNA are therefore suitable for epidemiological studies, but it has a limited ability to be used for comparison between studies. This limitation is due to differences in the DNA quality based on the method used for genomic DNA extraction and in sample fixation methods (357). Aviv et al has shown positive correlation for the quantitative PCR method between the replicate measures ($r > 0.9$), but the coefficient of variation value for the quantitative PCR method between two laboratories was 6.45%, compared to the TRF method for which the coefficient of variation was 1,74 % (358).

With fluorescence in situ hybridisation, FISH, using fluorescent probes not only mean telomere lengths can be quantified, but also chromosome-specific

telomere lengths (359). However, it can only be used on mitotically active cells and it is needs a lot of work and it is therefore not well suitable for large, epidemiological studies.

2.6.4 FACTORS ASSOCIATED WITH TELOMERE LENGHT

There are no differences between male and female new-borns in telomere length (TL), and variations in telomere length among new-borns are as wide as among adults (360). General heritability is proposed to be the major mechanism explaining interindividual TL variation. A meta-analysis has shown TL to be both maternally and paternally inherited and the heritability estimates to be 70 % (361). Higher paternal age at conception of the offspring has shown to be associated with longer offspring leucocyte telomere length (LTL) (362). Telomere shortening during cell division is reflected in an age-dependent telomere attrition at the systemic level, providing a second main cause of variation between subjects (363).

While there is no significant gender-dependent difference in TL at birth, and as the telomeres in adulthood are longer in women than in men (364) the gender difference has to arise from a slower rate of telomeric attrition in women. The most likely reason for this effect is estrogen. The effect of estrogen on telomere attrition during extra uterine life may be exerted in two ways. First, estrogen can stimulate telomerase, (365) the reverse transcriptase enzyme that elongates telomeres by adding telomeric repeats onto the ends of chromosomes. There is an estrogen response element in the catalytic unit of telomerase. Second, estrogen reduces oxidative stress, and reactive oxygen species has shown to accelerate the rate of telomere attrition (366).

TL has shown to be associated with many age-related diseases and chronic conditions, such as insulin resistance, hypertension, coronary heart disease, chronic heart failure and dementia (33-35, 367). Shorter telomeres has also been associated with many unhealthy lifestyles, like use of tobacco (29) and alcohol (32), unhealthy nutrition (32), obesity (30) and sedentary lifestyle (31) and also with life stress (28). Oxidative stress (368) and systemic inflammation (369) has been associated with shorter telomeres and the

underlining mechanism of many of the above-mentioned associations can be increased systemic inflammation.

2.6.5 PHYSICAL ACTIVITY AND TELOMERE LENGHT

There is inconclusive evidence of the association between physical activity and telomere length. Many cross-sectional studies have reported a significant association between both objectively measured and questionnaire based physical activity and longer telomere length (370-372). However, many studies have not reported a significant association (373, 374). A study investigating telomere length differences between young elite athletes and healthy non-smokers, physically inactive controls, found that elite athletes had, on average, higher LTL than control subjects (375). There are only a few longitudinal studies done exploring the association of physical activity with telomere length, and these have also reported inconsistent results. One study has reported that baseline physical activity was not associated with change in telomere length but changes in leisure-time activity was inversely associated with changes in telomere length (376). There are also interventional studies that have examined the potential influence of physical activity on telomere length, but these studies have not fully established such a relationship (377).

A systematic review from year 2015 including 37 studies did not found a significant association between physical activity and telomere length in 20 studies, while 15 studies described a positive association and in two studies the association was an inverted ”U” (378). In the meta-analysis, in 11 of these studies association between the level of physical activity and telomere length was not statistically significant. In the meta-analysis of 15 studies, that reported difference in the standardized means had a tendency for larger telomeres in the active group, although this finding was highly heterogeneous (378).

Dillard et al showed in 1978 that muscular exercise is associated with oxidative stress in humans (379). Both prolonged endurance exercise or short-duration, high intensity exercise has shown to result in an acute increase in biomarkers of oxidative stress and inflammation in both blood and skeletal muscle (380-382). On the other hand, continuous practise of physical activity

can improve the anti-oxidant activity and benefit the free radicals and cellular oxidoreductive balance, and also improve the inflammation balance (382, 383). This could explain the inverted ”U” shape of the association between physical activity and telomere length that some studies have reported (384). Both cardiac and skeletal muscles are plastic and continuous exercise training promotes an increase in antioxidant enzymes in cardiac and skeletal muscles and exercise-induced oxidant production is likely to contribute to the allosteric down-regulation of the activities of key metabolic enzymes (385, 386).

Oxidative stress is defined as an imbalance between oxidants and antioxidants in favour of the oxidants, leading to a disruption of redox signalling and control and/or molecular damage (387). Redox status of muscle fibers has shown to contribute to muscle fatigue and to modulate muscle force production and maximal force production in skeletal muscle fibres occurs at an optimal redox state (388). This ‘inverted U’ curve describes also the relationship between redox status and muscle force generation.

There are different proposed mechanisms to explain how exercise improves the redox status. Skeletal muscles consume large quantities of oxygen and can generate a great amount of ROS. ROS are generated in mitochondria during normal respiration but can also be produced in response to other kind of stimuli like such as growth factors, inflammatory cytokines, ionizing radiation, ultraviolet radiation, metal toxicity, chemical oxidants, chemotherapeutics, hyperoxia and toxins (389, 390). There are several enzymes participate in ROS generation (391). Under physiological conditions, oxidative stress is neutralized by the antioxidant system, which includes endogenous and exogenous molecules (390, 392). The antioxidants maintain muscle redox status. Exercise can alter the redox status by increasing the genetic expression of antioxidant proteins and increase in the DNA-repairing enzymes (393, 394). A mechanism by which physical activity regulates the anti-inflammatory balance is through reduction in C-reactive protein, interleukin-6, and tumour necrosis factor α levels (395, 396).

Another possible explanation for the relationship between physical activity levels and telomere length is the release of irisin, that is a hormone-like myokine produced by skeletal muscle in response to exercise (397). Plasma

irisin levels has shown to be positively associated with telomere length in healthy adults (398). At least in mice irisin has been shown also to increase brown adipose tissue leading to increased energy expenditure via thermogenesis and increased formation of brown fat has been shown to have anti-obesity and anti-diabetic effects (399).

3 AIMS OF THE STUDY

The general aims of this study were to investigate the association between physical activity in old age with physical performance and quality of life and aging.

Specific aims of this study were as follows:

1. How objectively measured physical activity is associated with physical performance in old age (I).
2. To assess whether birth weight modulates the association between physical activity and physical performance in old age (II).
3. To examine prospectively over a 10-year follow-up how change in self-reported leisure-time physical activity (LTPA) is associated with change in health-related quality of life (HRQoL) and symptoms of depression in old age (III).
4. To examine how self-reported LTPA is associated with leukocyte telomere length (LTL) and with change in LTL during a 10-year follow-up in old age (IV).

4 MATERIALS AND METHODS

4.1 SUBJECTS

All the studies (I-IV) included in this doctoral thesis utilize data from the HBCS. The original cohort includes 13,345 individuals born in Helsinki between 1934 and 1944 at one of the two public birth hospitals (Helsinki University Hospital and Midwives' Hospital), visited child welfare clinics in the city, and lived in Finland in 1971 when a unique personal identification number was assigned to all Finnish residents, which was used to link the individuals to register data. The birth records contain data on the mothers as well as their new-born babies. Records from child welfare clinics and school health care include serial measurements of weight and height. On average, the participants had 11 measurements between birth and two years, and 9 measurements between 2 and 11 years.

Of the cohort members who were born at the Helsinki University Hospital (n=8760), a random sample of 2902 were invited to take part in a clinical examination in the year 2000 in order to reach for a target of 2,000 participants for a clinical examination in the years 2001–2004. During 2001-04, 2003 cohort members participated in clinical measurements and interviews and data were gathered on physical, mental and cognitive functioning, lifestyle and social factors and diseases. From this clinical study cohort (n=2003), 1404 participants who were alive and lived within 100 km distance from the study clinic in Helsinki, were invited to participate in a second clinical examination in 2011. Participants (n=1094) attended this second clinical examination between 2011 and 2013. Individual who declined to participate did that mostly due to own or a family member's health conditions. The clinical cohort has been followed up also in 2017-18. The later data collection waves include rich data on factors related to healthy aging.

Figure 5 shows the formation of the samples for studies I-IV. In studies I and II the study includes of 695 of the total 1094 participants who attended the clinical examination between 2011 and 2013. These 695 individuals (316 men and 379 women) had information on both objectively measured physical

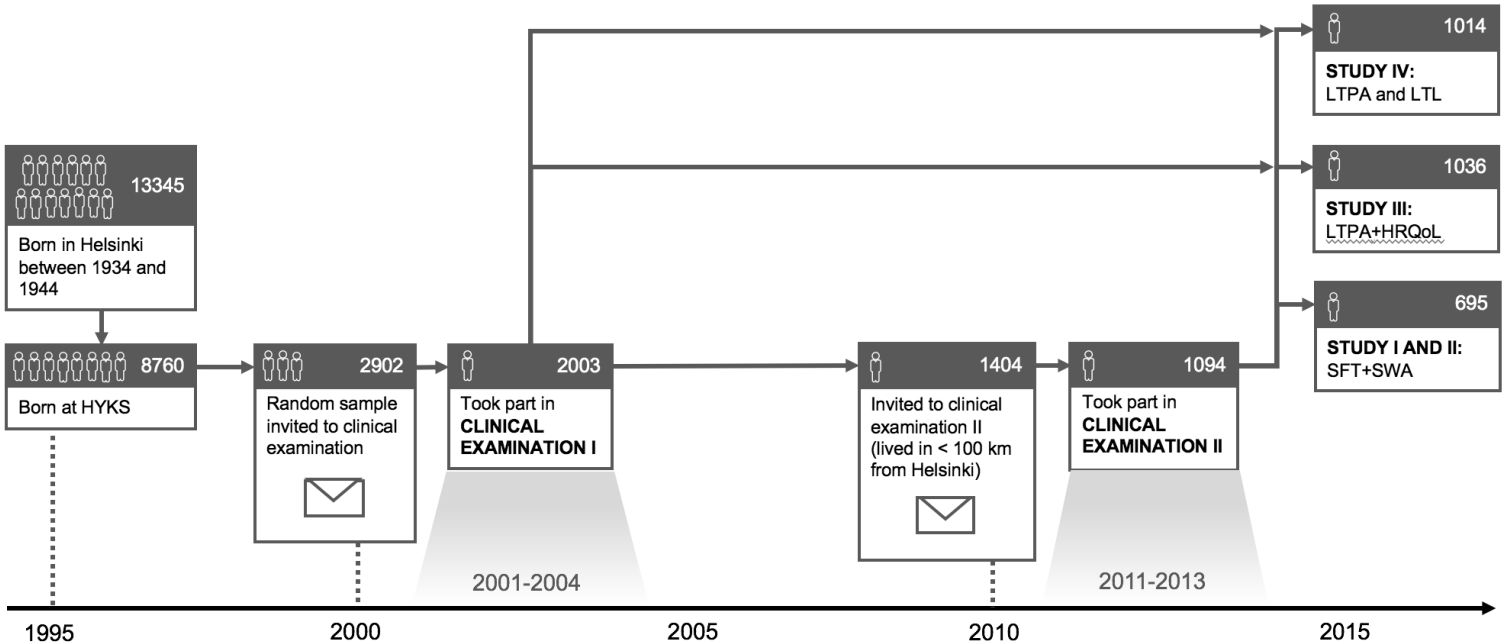

Figure 5 Study participants.

activity and physical performance test (SFT) and were included in these studies.

Study III includes 1036 individuals (457 men and 579 women) who took part to the clinical examinations in 2001-2004 and 2011-2013 and had information on both LTPA and HRQoL. Of individuals who had information on LTPA, 892 participants also had information on depressive symptoms.

Study IV includes 1014 individuals (445 men and 569 women) who took part in both clinical examinations in 2001-2004 and 2011-2013 and who had information on LTPA in 2001-2004 and on telomere length both in 2001-2004 and in 2011-2013.

The clinical study protocols were approved by the Ethics Committee of Epidemiology and Public Health of the Hospital District of Helsinki and Uusimaa and the Coordinating Ethical Committee of the Hospital District of Helsinki and Uusimaa. Written informed consent was obtained from each participant before any study procedure was initiated.

4.2 MEASUREMENTS

4.2.1 PHYSICAL MEASUREMENTS

At each clinical visit height was measured with a KaWi stadiometer; weight with SECA alpha 770 (Brooklyn, NY, USA) scales. Height and weight were measured in light indoor clothing and without shoes. Height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg. Body mass index (BMI) was calculated as weight in kilograms divided by square of height in meters (kg/m^2). Body composition was assessed with bioelectrical impedance by using the InBody 3.0 eight-polar tactile electrode system (Biospace Co., Ltd., Seoul, Korea).

Data on the mothers and their new-born babies were retrieved from the birth records at Helsinki University Hospital. Data on the mothers include age, parity, height, and date of the last menstrual period, together with body weight measured on admission in labour. Data on the new-born babies include birth weight, placental weight, length, and head circumference. Birthweight and

placental weight were rounded to the nearest 5 g and length and head circumference to the nearest 0.5 cm.

Data on reproductive history, including age at menarche and menopause, were assessed by questionnaires. Duration of reproductive life in years was computed as the difference between age at menopause and menarche. It was used as a surrogate for the length of endogenous estrogen exposure.

4.2.2 LABORATORY MEASUREMENTS

Venous blood samples were taken in the morning after twelve hours of fasting from the brachial vein in a sitting position. All laboratory tests were performed using in-house methods and standard accredited assays.

LTL was measured twice, at the time of the first clinical examination in 2001–2004, and at the follow-up examination in 2011–2014. DNA was extracted from peripheral whole blood using a commercially available kit according to the manufacturer's instruction (QIAamp blood Maxi kit and DNeasy blood and tissue kit, Qiagen s.r.l. (Venlo, The Netherlands) respectively). The concentration and purity of DNA were assessed by comparing ultraviolet absorbance at wavelengths of 260 nm to absorbance at 230 nm (260/230 ratio) for salts contamination, and to 280 nm (260/280 ratio) for other contaminants, including proteins. Samples, which ratios were ranging between 1.7 and 2.1, were considered pure and suitable for the following steps. The integrity of DNA was tested by electrophoresis in 0.8% agarose/0.5x TBE with 0.1 μL/mL Ethidium bromide at ~100 V for 15–25 minutes.

LTL was measured from DNA extracted from peripheral blood using quantitative real-time polymerase chain reaction (qPCR) (355). At the first examination (in 2001-2004), relative telomere length was determined as the ratio of telomere DNA to β-haemoglobin single-copy gene signal intensities. Based on O'Callaghan's method (400) a synthetic oligomer Sigma (St Louis, Missouri, USA) dilution series, hbg-120-mer and tel14x, was included in every plate to create reaction-specific standard curves, and plasmid DNA (pcDNA3.1) was added to each standard to maintain a constant 10 ng of total

DNA concentration per reaction. Quality control was carried out with the Bio-Rad CFX Manager software v.1.6 9 (Bio-Rad Laboratories, Hercules, CA, USA). All plates included four genomic DNA control samples for the plate effect calibration and for monitoring the coefficient of variation, which was 21.0% for the telomere reaction, 6.0% for the β- haemoglobin reaction, and 24.8% for their ratio (T/S). The plate effect was taken into account by normalizing the telomere signal and reference gene signal to the corresponding mean of four control samples that were analysed for every qPCR plate before taking the T/S ratio (telomere reaction and β-haemoglobin reaction ratio). Three outlier samples of T/S ratio were removed before statistical analyses.

At the second examination (in 2011-2013), the multiplex quantitative real-time PCR method was used to measure the relative telomere length as described by Cawthon (401) and modified by Guzzardi et al (402). DNA concentration was standardized to 4 ng/μL and combined with telomere primers pair 900 nM, beta-globin (as single-copy gene) primers pair 500 nM, and 2X master mix (IQ Sybr green supermix, Bio-Rad Laboratories). PCR reactions were set up in a 384-well plate (CFX384 Touch Real-Time PCR detection system, Bio-Rad Laboratories) and carried out in a final volume of 10 μL. The original thermal cycle (401) was used. A 1:3 serial dilution curve was run to assess the efficiency of the amplification. Threshold cycles (Ct) for both telomere and beta-globin amplification were analysed using a dedicated software (CFX Manager software, Bio-Rad Laboratories). This method provided a relative telomere length (T/S) ratio that is expressed as the ratio between the amplification of the telomere sequence (T) and that of a single copy gene (S). These were measured for each sample in the same PCR run and normalized using a common reference DNA sample. Samples were run in triplicate; the mean coefficient of variation of each triplicate was 6.0%, and the mean inter-assay CV% was 6.2%.

4.2.3 LIFESTYLE FACTORS

At the clinical examinations, participants' chronic diseases, smoking habits and other health characteristics were assessed by questionnaires. The history

of smoking was expressed as years of smoking. Data on educational attainment expressed as years of studying was obtained from Statistics Finland. For study III we calculated a comorbidity score. It was calculated by summing up the number of the following diseases/symptoms obtained from the questionnaire at the first clinical examination: myocardial infarction, angina pectoris, congestive heart failure, claudication, osteoporosis, stroke, depression, asthma or emphysema.

4.2.4 PHYSICAL FITNESS TEST

In study I and II the physical fitness of 695 participants was assessed between 2011 and 2013 by using a validated Senior Fitness Test battery (SFT) (242, 243). We used five test components of the six fitness test components originally included in the SFT (403). The 30-second chair stand test consists of the number of full stands from a seated position with arms folded across the chest which can be completed in 30 seconds. Its purpose is to assess lower-body strength needed for numerous every-day tasks such as climbing the stairs, getting out of a chair and walking. The 30-second arm curl test consists of several bicep curls that can be completed in 30 seconds while holding a hand weight of 2 kg for women and 3 kg for men. Its purpose is to assess upper-body strength needed to perform activities that involve lifting and carrying things such as groceries and grandchildren. In the chair sit and reach test the patient is seated in a chair with legs extended at front of the chair and is instructed to keep the back straight and reach the toes with both hands. The number of centimetres between the extended fingers and the tip of the toe is measured. The purpose of the test is to assess lower-body flexibility, which is important for good posture, normal gait patterns and to get in and out from a car. The 6-minute walk test consists of the number of meters walked in 6 minutes and it measures the aerobic endurance. In the back scratch test, the subject puts one hand over the same shoulder with the palm touching the back and reached down the back. The other hand is placed up the back from the waist with the palm facing outwards. The number of centimetres (+ or -) between extended middle fingers is measured. The purpose of the test is to assess upper-body

flexibility which is needed in tasks such as combing the hair, putting on garments and reaching for seat belt.

For each test, the scores of the participants were also classified with respect to percentile tables of normative data for each 5-year age group (243). The result of each test was expressed as age (for each 5-year group) and sex standardized percentile scores. A rating from 1 to 20 was given according to each 5-percentile range, with 1 being the worst performance (score below the 5th percentile), 2 the score from the 5th to the 9th percentile, and 20 the best performance (in or above the 95th percentile). An overall score was calculated by summarizing the normalized scores of the five SFT components. The overall SFT score varied between 5 and 100.

The SFT has been shown to be reliable (242), also in older people with cognitive impairment (404) and it has been validated. The criterion validity of SFT components varies between 0.73-0.83 and the test-retest reliability between 0.80-0.98 (242). Rikli et Jones have also developed and validated reference standards for men and women ages 60-94 indicating the level of capacity needed for maintaining physical independence into later life (243). Reliability and validity indicators for the standards is ranging between 0.79 and 0.97 (243).

4.2.5 OBJECTIVELY MEASURED PHYSICAL ACTIVITY

In order to obtain objectively measured physical activity in studies I and II, participants were instructed to wear a multisensory body monitor, the SenseWear Pro 3 Armband (SWA) (BodyMedia, Inc., Pittsburg, PA, USA). The physical activity measurements were done between 2012 and 2013. The SWA is a multisensory body monitor that enables continuous collection of various physiological and movement parameters through multiple sensors, including the measurements of skin and near-body temperature, galvanic skin response, heat flux and biaxial accelerations. It was worn on the triceps of right arm. Data collected by these sensors are combined with subjects' characteristics including gender, age and BMI to estimate energy expenditure (EE), intensity of physical activity and number of steps, using algorithms developed by the manufacturer (Innerview SenseWear Professional software, version 6.1).

Participants were instructed to wear the body monitor for 10 consecutive days, 24 hours per day. They were instructed to take off the SWA only for showering, bathing and water exercise, as the SWA is not waterproof. Participants who had valid data from at least four weekdays and one weekend day were included in the analysis. If the participant had more than 5 valid days, the days with the highest amount of data (most measured minutes) were chosen. A valid day consisted of a day with at least 1296 minutes of data, which corresponds to 90% of a whole 24-hour period. To standardize the measurement period to 24 hours across individuals, a 1 metabolic equivalent of task (MET, 1 MET = 3.5 ml O2/kg/min or 1 kcal/kg/h), which corresponds to the metabolic rate of sitting at rest, was added for every missing minute.

The PA derived from the SWA was expressed in metabolic equivalents of task (MET). MET values were multiplied with time (hours) to calculate MET-hours. The SWA software allows researchers to select physical activity at any metabolic equivalent (MET) level. We divided the daily averages of physical activity into three intensity levels, sedentary time (ST) < 1.5 MET, light physical activity > 1.5–< 3.0 MET and moderate to vigorous (MVPA) >3 MET. We used pre-defined cut-off values that doesn't take into account individual's level of fitness. The SWA is shown to be valid in assessing EE in free-living conditions (405).

Self-reported LTPA was assessed at both the first clinical examination in 2001-2004 and the follow-up clinical examination in 2011-2013. Study III used the information of LTPA of 1036 participants at both examinations. In study IV study the information of LTPA of 1014 participants from the first examination in 2001-2004 was used. LTPA was self-reported by using the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study. It is a validated LTPA history questionnaire on 12 months (406, 407). The KIHD questionnaire is a modification of the Minnesota leisure time activity questionnaire. In the KIHD questionnaire a list of different kinds of PA is presented (Figure 6). The list includes conditioning LTPA e.g. jogging, team games, skiing, swimming; non-conditioning LTPA e.g. picking berries, shovelling snow; PA from commuting to work by walking or cycling and a category for "other" physical activities that could be specified by the

participant. In the questionnaire participants had to fill in frequency expressed as occasions per month, average duration expressed as minutes or hours and intensity of each activity he/she has performed during the previous 12 months. The intensity of the activity was classified as recreational, conditioning, brisk conditioning or competitive, strenuous exercise. A MET value (MET, 1 MET = 3.5 ml $O2 \cdot kg^{-1} \cdot min^{-1}$ or 1 $kcal \cdot kg^{-1} \cdot h^{-1}$) was determined for each activity and intensity class based on the compendium of physical activities by Ainsworth et al (52, 408). The volume of LTPA was expressed in MET hours per week, which was calculated by multiplying the intensity (MET) with the average duration and frequency of activities.

FINNISH INSTITUTE OF HEALTH AND WELFARE **IDEFIX 2011-12**

Date _____ / _____ 20_____

Name: _____

LEISURE-TIME PHYSICAL ACTIVITY QUESTIONNAIRE

Which of the following sport or physical exercise have you practiced the past 12 months?

Please rate the usual intensity of your physical activity by choosing one alternative of the following category.

Category	Type of exercise	Grade of breathless	Grade of sweating
0	Recreational	Not breathless	Not sweating
1	Conditioning	Breathless	Not sweating
2	Brisk conditioning	Breathless	Somewhat sweating
3	Competitive, strenuous	Breathless	Sweating a lot

Activity	How many times per month?												Time on average (h, min)	Intensity (0-3)
	January	February	March	April	May	June	July	August	September	October	November	December		
Walking to/from work														
Walking														
Jogging														
Cross-country skiing														
Cycling														
Cycling to/from work														
Swimming														
Conditioning exercise/dance														
Ball games														
Gardening, shovelling snow														
Hunting, berry-picking														
Fishing														
Home repair, hobby crafts														
Rowing (conditioning, distance)														
Forest work, woodcutting														
Other, specified														

Figure 6 12-month LTPA history questionnaire.

4.2.6 MEASURING HEALTH-RELATED QUALITY OF LIFE

In study III, HRQoL was assessed at the clinical examinations in 2001-2004 and 2011-2013 by the Finnish validated version of RAND 36-Item Health Survey 1.0 (Short Form 36 (SF-36)) (292, 409, 410). The SF-36 is a self-administered questionnaire. It has been found to be a reliable and valid measure of health-related quality of life in the Finnish population (410) and also in older people (224, 411). It is divided into eight domains that measures physical functioning, role limitation due to physical problems, bodily pain, general health perception, vitality, social functioning, role limitation due to emotional problems and mental health. Each subscale includes 2-10 questions, which are scored on a scale from 0 to 100, where 0 stands for unable to perform or a lot of problems, 50 stands for some problems and 100 stands for no problems. We grouped these eight domains in physical and mental components providing physical component summary (PCS) and mental component summary (MCS) scores by using a US reference population (1990) for standardization of the eight domains and for factor score coefficients (297). We standardized the mental and physical components using a mean of 50 and a standard deviation of 10 (in the US population) according to the "SF-36 Physical and Mental Health Summary Scales: A User's Manual" to allow comparison between the participants and meaningful interpretation of the scores (294). US population was chosen to make it comparable to the other studies. This will not affect the findings, but their interpretation. The dimensions physical functioning, role physical, bodily pain and general health form the PCS, and mental health, vitality, social functioning and role-emotional the MCS.

4.2.7 ASSESSMENT OF SYMPTOMS OF DEPRESSION

In study III, symptoms of depression was screened by using the Beck's Depression Inventory (BDI) (412). 892 participants of the study group (n=1036) had answered the BDI questionnaire on depressive symptoms at both clinical examinations in 2001-2004 and 2011-2013. BDI is a self-report rating inventory and it is composed of 21 multiple-choice questions. Each question has four possible responses. Each response is assigned a score

ranging from zero to three, indicating the severity of the symptom. Questions assess mood, pessimism, sense of failure, self-dissatisfaction, guilt, punishment, self-dislike, self-accusation, suicidal ideas, crying, irritability, social withdrawal, body image, work difficulties, insomnia, fatigue, appetite, weight loss, bodily preoccupation, and loss of libido. Items 1 to 13 assess symptoms that are psychological in nature, while items 14 to 21 assess more physical symptoms. It is developed to measure the intensity, severity, and depth of depression. BDI has been originally developed to detect, assess, and monitor changes in depressive symptoms among people in a mental health care setting, but can be also used to detect depressive symptoms in a primary care setting. To complete BDI usually takes between ten and fifteen minutes.

Totalling the numbers of each question gets the score and the sum of all BDI item scores indicates the severity of depressive symptoms. However, a diagnosis of depression cannot be made with it. The score varies between 0-63. A score ≥ 10 signifies the presence of clinical depression (413). BDI has shown to be valid and reliable instrument for measuring the severity of depressive symptoms (414).

4.3 STATISTICAL ANALYSIS

The statistical analyses were carried out using SPSS (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp) and Stata/SE 14.2 (StataCorp LP, College Station, TX, USA).

Data is presented as means with standard deviations (SD) or 95% confidence intervals (CI). Statistical comparisons between groups were conducted by using analysis of variance (415) or with Student's t test.

In study I multiple linear regression analyses were used to assess the association between the volume of daily physical activity and SFT overall and component scores. The volume of daily physical activity was assessed as total physical activity, sedentary time, light physical activity and MVPA. The SFT components were chair stand test, arm curl test, chair sit and reach test, six min walk test and back scratch test. In the analyses standardized SFT scores was used.

In study II we used linear regression analyses to assess the association between physical activity and physical performance in different birth weight groups. We expressed the results as standardized regression coefficients Beta (β). The Beta value tells how strongly the predictor variable influences the criterion variable. The standardized coefficients refer to how many standard deviations a dependent variable will change, per standard deviation increase in the predictor variable. Cohen's standard for Beta values for defined as: small = 0.10-0.29, moderate = 0.30-0.49 and large ≥ 0.50 relationships.

In study III we assessed the association between LTPA at baseline and the change in PCS, MCS and BDI in ten years with multiple linear regression analyses. We also used multiple linear regression analyses to assess the associations between standardized (β) change in the total volume of LTPA and the change in PCS, MCS and BDI. The change in LTPA was applied both as a continuous and categorical variable. The standardized LTPA change was divided into tertiles according to <-0.5 SD, -0.5 to 0.5 SD and >0.5 SD.

For the analyses of study IV both men and women were divided into quartiles according to the volume of LTPA at baseline. Multiple linear regression analyses were applied to assess the association between LTPA quartiles and LTL at baseline. We also assessed the association between LTL quartiles and the relative and residual LTL change in 10-year follow-up.

5 RESULTS

5.1 OBJECTIVELY MEASURED PHYSICAL ACTIVITY, PHYSICAL PERFORMANCE AND BIRTH WEIGHT (STUDY I AND II)

5.1.1 CHARACTERISTICS OF STUDY POPULATION

Tables I and II show the characteristics of the participants in study I and II men and women separately. The mean age (SD) of the 695 participants was 70.7 years (2.7). There was no significant gender difference in the age or BMI, but men had larger lean body mass and women had higher body fat percentage (p<0.001 for both). Men had significantly higher birth weight than women (3480.4 g and 3370.7 g respectively, p=0.002), but there was no significant difference in the gestational age between men and women (279.3 days vs. 280.6 days, p=0.102).

Women succeeded better in SFT in overall and the mean SFT sum score were in women 48.7 and in men 43.7 (p<0.001). Women also had better scores in the chair stand, arm curl and chair sit and reach test than men (p<0.001, p=0.002 and p<0.001, respectively). In the six-minute walk test and in the back-scratch test there were no gender differences (p=0.503 and p=0.118 respectively). Total volume of physical activity and MVPA was higher in men than in women (p<0.001 in both), but men also had more sedentary time (p<0.001). On the other hand, women had more light physical activity (p=0.009).

The volume of physical activity did not differ between birth weight groups in men or in women (p=0.38 and p=0.50, respectively) (Table I and II). There was no difference in the mean SFT score between the birth weight groups in men or in women (p=0.15 in men and p=0.74 in women).

Table 1 Characteristics of men in study I and II.

	Total (*n*=316)		<3000 g (*n*=39)		3000-3499 g (*n*=130)		≥3500 g (*n*=147)	
Characteristics of men	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	70.6	2.6	71.3	2.4	70.7	2.7	70.4	2.5
Weight (kg)	83.3	13,0	82.8	11.3	82.6	12.2	84.2	14.1
Height (cm)	176.3	6.1	174.9	6.6	175.9	6.0	177.1	6.1
Body mass index (kg/m^2)	26.8	3.8	27.1	3.5	26.7	3.6	26.8	4.1
Lean body mass (kg)	63.5	7.6	62.2	6.8	63.0	7.3	64.3	8.1
Body fat (%)	23.3	5.9	24.5	5.8	23.3	5.4	23.0	6.3
Smoking (years)	15.5	17.7	15.1	18.6	14.5	17.2	16.4	17.9
Years of fulltime studying	12.9	3.8	13.2	4.1	12.7	3.7	13.1	3.8
SFT test results								
Sum Score (Contains 5 test)	43.7	16.8	39.7	17.1	43.0	16.5	45.3	16.9
Chair stand percentiles	29.3	15.7	25.6	15.0	28.7	15.5	30.9	15.8
ArmCurl percentiles	47.2	23.4	42.4	24.3	47.0	23.3	48.6	23.2
Chair sit and reach percentiles	38.1	28.6	35.4	30.9	36.1	27.6	40.5	28.8
Six min walk percentiles	55.6	27.6	49.0	28.7	55.1	27.4	57.7	27.4
Back scratch percentiles	48.2	29.9	46.3	29.7	48.3	29.8	48.6	30.2
Volume of PA (METmin/d)								
Total Volume	30.5	4.4	29.7	4.1	30.8	4.8	30.5	4.3
Volume of ST	16.9	1.3	17.2	1.6	16.8	1.3	16.9	1.1
Volume of light PA	7.9	2.6	7.4	2.9	8.1	2.5	7.9	2.7
Volume of MVPA	5.7	4.0	5.1	3.5	5.9	4.4	5.7	3.8
Birth weight (g)	3480	485	2662	253	3277	132	3877	319
Gestational age (d)	279.3	10.6	271.5	10.7	278.1	11.3	281.9	8.9

Abbreviations: SD, standard deviation; SFT, Senior Fitness Test, PA, physical activity; MET, metabolic equivalents of task; ST, sedentary time; MVPA, moderate to vigorous physical activity.

Table 2 Characteristics of women in study I and II.

	Total (*n*=379)		<3000 g (*n*=74)		3000-3499 g (*n*=150)		≥3500 g (*n*=155)	
Characteristics of women	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	70.8	2.7	71.1	2.6	70.7	2.7	70.9	2.7
Weight (kg)	71.6	12.7	68.6	11.2	70.6	11.8	74.0	13.8
Height (cm)	162.4	5.7	161.7	6.2	161.3	5.4	163.7	5.6
Body mass index (kg/m^2)	27.2	4.8	26.3	4.7	27.1	4.3	27.6	5.2
Lean body mass (kg)	46.1	5.3	44.6	4.7	45.2	5.2	47.7	5.3
Body fat (%)	34.8	6.7	34.3	7.0	35.2	6.1	34.6	7.1
Smoking (years)	7.8	14.6	8.7	15.7	7.7	14.3	7.5	14.5
Years of fulltime studying	12.3	3.4	11.9	3.1	12.4	3.6	12.4	3.5
SFT test results								
Sum Score (Contains 5 test)	48.7	17.8	47.8	16.8	48.2	17.7	49.5	18.4
Chair stand percentiles	33.6	20.1	35.2	19.4	34.5	20.4	32.0	20.2
ArmCurl percentiles	53.1	23.6	49.5	21.8	53.4	23.8	54.5	24.1
Chair sit and reach percentiles	51.1	29.6	49.8	30.9	49.8	29.7	53.0	28.9
Six min walk percentiles	54.2	26.8	55.0	27.3	54.0	25.8	54.0	27.6
Back scratch percentiles	51.7	28.9	50.1	29.1	49.9	28.1	54.3	29.7
Volume of PA (METmin/d)								
Total Volume	28.9	5.3	29.5	5.0	29.0	5.1	28.6	5.6
Volume of ST	16.1	1.3	16.2	1.5	16.1	1.3	16.0	1.3
Volume of light PA	8.6	3.3	9.1	3.4	8.5	3.1	8.3	3.4
Volume of MVPA	4.3	3.6	4.3	3.1	4.3	3.6	4.3	3.8
Birth weight (g)	3370	450	2754	203	3221	141	3810	244
Gestational age (d)	280.6	10.6	277.3	11.9	279.4	10.2	283.3	9.7

Abbreviations: SD, standard deviation; SFT, Senior Fitness Test, PA, physical activity; MET, metabolic equivalents of task; ST, sedentary time; MVPA, moderate to vigorous physical activity.

5.1.2 RELATIONSHIP BETWEEN OBJECTIVELY MEASURED PHYSICAL ACTIVITY AND PHYSICAL PERFORMANCE

Total volume of physical activity, light physical activity and MVPA were associated with total score of SFT both in men and women (total volume β=0.08., CI 0.06-0.10, p<0.001 for men and β=0.09, CI 0.07-0.10, p<0.001 for women, light physical activity β=0.07, CI 0.03-0.11, p=0.001 for men and β=0.11, CI 0.08-0.14, p<0.001 for women and MPVA β=0.08, CI 0.06-0.11, p<0.001 for men and β=0.11, CI 0.09-0.14, p<0.001 for women). Sedentary time (ST) was inversely associated with total SFT score both in men and women (β=-0.14, CI -0.22 - -0.05, p<0.001 for men and β=-0.11, CI -0.19- -0.04, p=0.004 for women). Men and women were grouped together for further analyses, because there were no gender differences in the results. In Figure 7 is shown the association between volume of total physical activity and the different components of SFT. All test components of SFT were also associated (adjusted for age) with total volume of physical activity, light volume of physical activity and with MVPA. ST was inversely associated with chair stand, arm curl and six-minute walk test components, but not with chair sit and reach and with back scratch components (β for chair sit and reach -0.05, p=0.078 and β for back scratch 0.04, p=0.145). The results were not attenuated when further adjusted for smoking and educational attainment.

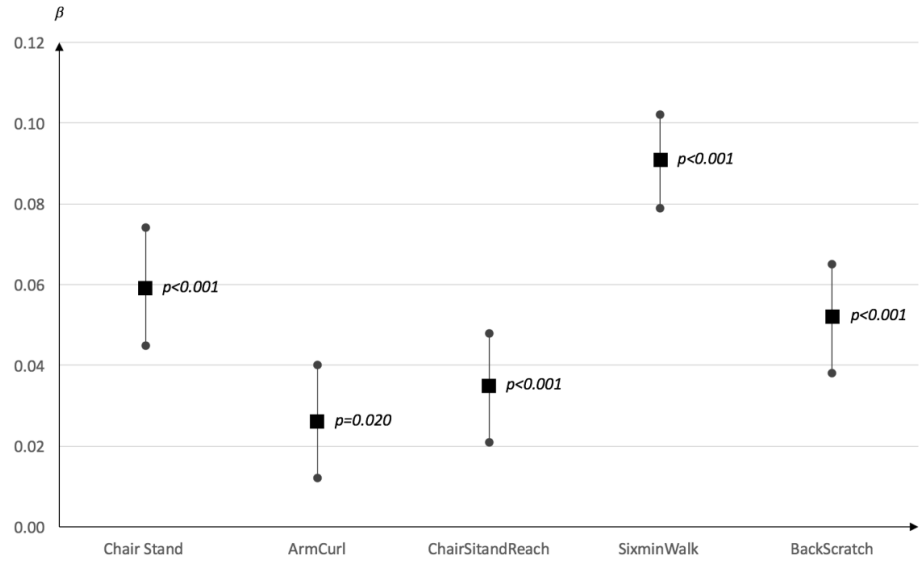

Figure 7 The association between volume of total physical activity and the different components of Senior Fitness Test (SFT). Multiple linear regression adjusted for age and sex. The dots give 95 per cent confident intervals.

5.1.3 RELATIONSHIP BETWEEN PHYSICAL ACTIVITY AND PHYSICAL PERFORMANCE IN DIFFERENT BIRTH WEIGHT GROUPS

When the study population was divided into three groups according to the birth weight (<3000 g, 3000-3499 g and ≥3500 g), there still was a significant association between total volume of physical activity and the SFT score (adjusted for age, gestational age, studying and smoking years) in each of the birth weight group both in men and women. Figure 8 shows the associations in quadric polynomial regression fit between physical activity and physical performance in different birth weight groups men and women separately. The association was large based on Cohen's standard only in men whose birth weight were <3000 g (β=0.59, CI 0.37-0.81, p<0.001).

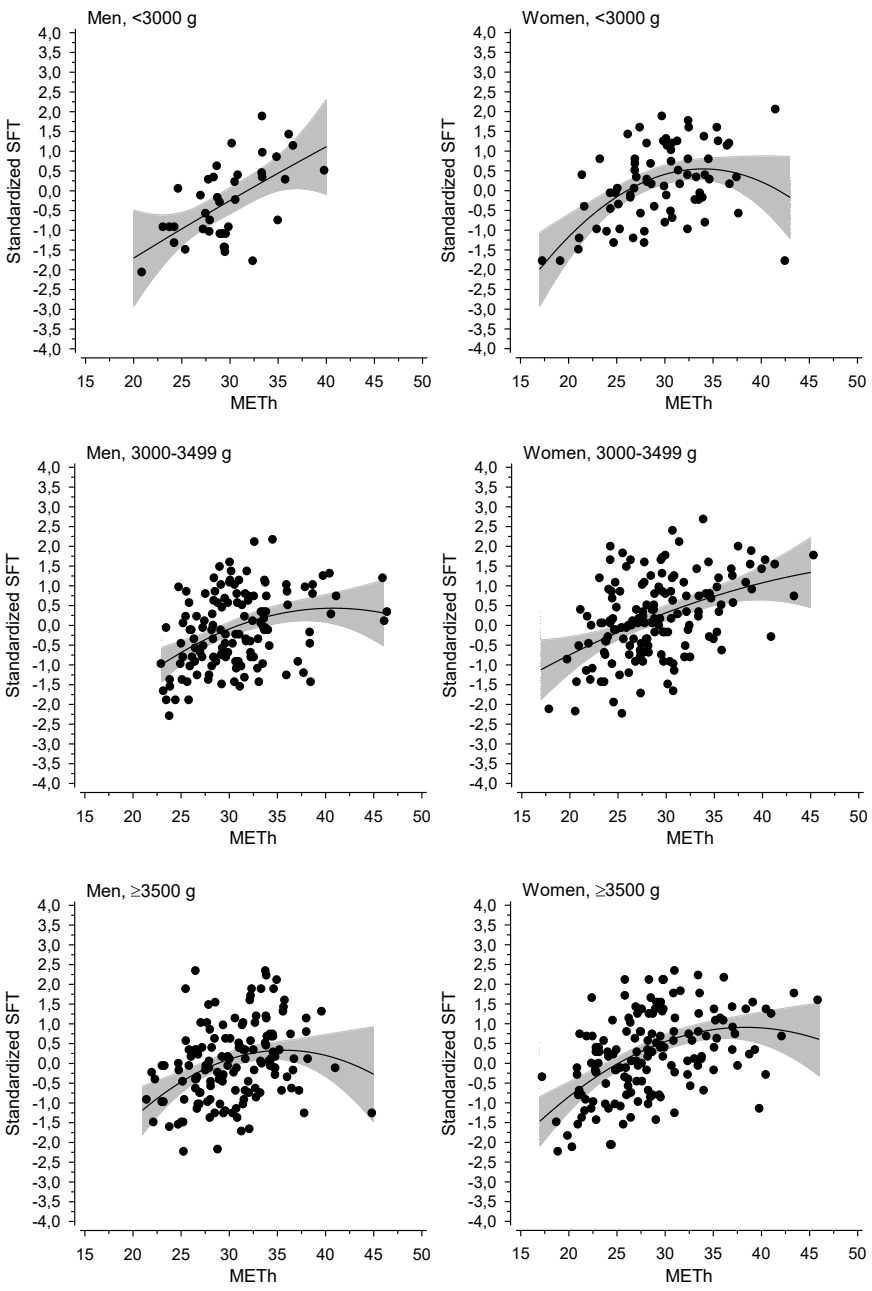

Figure 8 The associations (quadric polynomial regression fit) between physical activity (METh) and physical performance (standardized SFT) in different birth weight groups men and women separately. The grey area gives 95 per cent intervals. Reproduced with permission of Journal of Developmental Origins of Health and Disease.

5.2 PHYSICAL ACTIVITY AND HEALTH-RELATED QUALITY OF LIFE (STUDY III)

5.2.1 CHARACTERISTICS OF THE STYDY POPULATION

Table 3 shows characteristics of the study population in study III separately for men and women. The mean age of the 1036 participants in study III was 62.1 years (range 56.8-69.8 years). At baseline, there was no differences between volume of LTPA between men and women (46.9 METh/week vs. 45.8 METh/week respectively, p=0.622), but at follow-up men reported greater volume of LTPA than women (39.7 METh/week vs. 29.3 METh/week, p<0.001). At both time points men had better results both in the mental and physical component of SF36 (p<0.001 for both) and women had higher scores in BDI than men (p<0.001).

Table 3 Characteristics of the study population in study III.

	Men (*N=457*)		Women (*N=579*)		
Characteristics	Mean	SD	Mean	SD	p[a]
Age (years)	61.2	2.6	61.3	2.9	0.592
Smoking (years)	15.1	15.6	7.7	13.3	<0.001
Years of fulltime studying (years)[b]	13.0	3.8	12.3	3.5	0.001
Comorbidity score, n / (%)[c]					0.254
No comorbidities	346	(76)	415	(72)	
1 comorbidity	84	(18)	120	(21)	
≥2 comorbidities	25	(5)	43	(7)	
Volume of LTPA at baseline (METh/wk)	46.9	37.5	45.8	37.1	0.622
Volume of LTPA (METh/wk) follow-up	39.7	37.8	29.3	30.5	<0.001
PCS at baseline	51.0	6.6	48.7	8.6	<0.001
PCS follow-up	48.6	8.2	46.5	9.0	<0.001
MCS at baseline	55.4	7.3	53.2	9.3	<0.001
MCS follow-up	55.9	7.1	53.9	9.1	<0.001
BDI at baseline[d]	4.2	4.0	6.1	5.1	<0.001
BDI follow up[d]	6.0	4.9	8.4	6.2	<0.001

Abbreviations: SD, standard deviation; LTPA, leisure-time physical activity; MET, metabolic equivalents of task; PCS, Physical Component Summary; MCS, Mental Component Summary; BDI, Beck Depression Inventory.

5.2.2 ASSOCIATION BETWEEN CHANGE IN LTPA AND HEALTH-RELATED QUALITY OF LIFE AND SYMPTOMS OF DEPRESSION

Baseline volume of LTPA was not associated with the change in the mental and physical component of SF36 (β for PCS = 0.01, 95 % CI = -0.01 to 0.02, p=0.235 and β for MCS = -0.01, 95 % CI = -0.02 to 0.004, p=0.150) or BDI (β = 0.006, 95 % CI = -0.004 to 0.02, p=0.213) during the ten year follow-up.

The association between standardized change in LTPA and PCS was significant both in men and women (B = 0.7, CI = 0.1 to 1.3, p=0.032 form men and B = 0.8, CI = 0.2 to 1.5, p=0.014 for women). In women, there was also an association between the standardized change in LTPA and MCS (B = 1.0, CI = 0.3 to 1.7, p=0.005), but not in men (B = 0.3, CI = -0.2 to 0.9, p=0.253). Also, in women an increase in LTPA was associated with lower BDI scores (B = -0.7, CI = -1.1 to -0.2, p=0.003), but this was not the case in men (B = -0.1, CI = -0.5 to 0.3, p=0.718).

When the change in LTPA was categorised in tertiles according to standardized LTPA change (<-0.5 SD, -0.5 to 0.5 SD and >0.5 SD), both in men and women a linear relationship was seen between change in LTPA tertiles and positive change in PCS (p for linearity 0.01 and 0.02 respectively) (Figure 9 A). In women, also a linear relationship was seen between change in LTPA and positive change in MCS (p for linearity 0.025) and with a negative change in BDI (p for linearity 0.036) (Figure 9 B and C). In men, there were no significant linear relationship between change in LTPA tertiles and change in MCS and BDI (p for linearity 0.47 for MSC and 0.75 for BDI) (Figure 9 B and C).

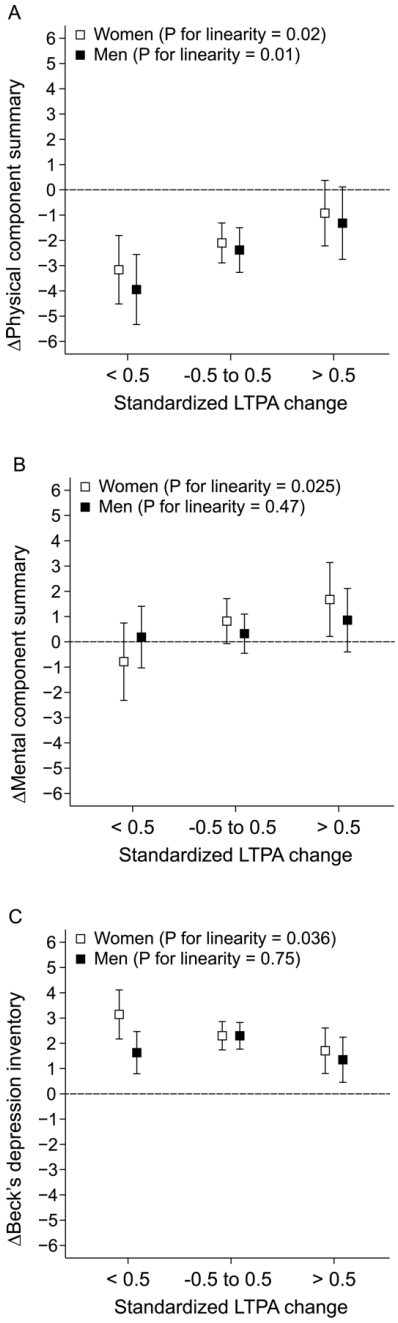

Figure 9 Change in the physical component summary score of SF36, mental component summary score of SF36 and Beck's Depression Inventory score according to standardized LTPA (METh) change tertiles during 10 years follow-up. Reproduced with permission of Scandinavian Journal of Medicine & Science is Sports.

5.3 PHYSICAL ACTIVITY AND TELOMERE LENGHT (STUDY IV)

5.3.1 CHARACTERISTICS OF STUDY POPULATION

Table 4 shows the characteristics of the study population according to LTPA quartiles for men and women. At the first clinical examination, the mean age of the 1014 participants of study IV was 61 years (range 56-69 years). Both men and women were divided into quartiles according to the volume of LTPA at the first clinical examination. In the upper LTPA quartiles the age of the participants was highest both in men and women (p for trend <0.001) and in women the fat percentage was lower (p for trend 0.004). In other characteristics, there were no significant differences between the LTPA quartiles.

Table 4 Characteristics of the study population in study IV according to LTPA quartiles for men and women.

LTPA quartiles	I	II	III	IV	P for trend
Men					
Number	110	112	111	112	
Total Volume of LTPA (METh/wk), median (IQR)	13 (8, 18)	27 (24, 32)	46 (41, 55)	88 (73, 107)	
Age (year), mean (SD)	60 (2)	61 (3)	61 (3)	61 (2)	<0.001
Percent body fat (%), mean (SD)	21.3 (8.1)	18.6 (5.6)	19.6 (6.7)	20.2 (7.4)	0.15
Years of fulltime studying, mean (SD)	12.8 (3.7)	13.0 (3.7)	13.7 (4.1)	12.7 (3.8)	0.75
Smoking years, mean (SD)	16.3 (16.4)	15.4 (15.8)	13.9 (15.1)	14.3 (15.0)	0.26
Women					
Number	142	142	142	143	
Total Volume of LTPA (METh/wk), median (IQR)	13 (9, 17)	29 (25, 32)	46 (40, 51)	83 (68, 108)	
Age (years), mean (SD)	60 (3)	60 (3)	61 (3)	62 (3)	<0.001
Percent body fat (%), mean (SD)	26.0 (9.4)	24.5 (8.9)	23.6 (8.2)	23.7 (8.7)	0.004
Years of fulltime studying, mean (SD)	12.2 (3.4)	12.6 (3.7)	12.2 (3.5)	11.8 (3.2)	0.27
Smoking years, mean (SD)	8.2 (14.1)	7.9 (14.1)	7.7 (12.9)	7.1 (12.6)	0.47
Duration of reproductive life in years, mean (SD)	38.0 (4.7)	37.2 (5.0)	36.2 (5.5)	37.2 (4.7)	0.065

Abbreviations: LTPA, leisure-time physical activity; MET, metabolic equivalents of task; IQR, interquartile range; SD, standard deviation.

5.3.2 ASSOCIATION BETWEEN LTPA AND LEUCOCYTE TELOMERE LENGTH

At baseline, there were no significant association between volume of LTPA and LTL in men or women (p=0.66 and p=0.33, respectively). The analyses were adjusted for age, educational attainment, smoking years, body fat percentage and length of reproductive life in women. Further adjustment for hormone therapy use (dichotomic) did not attenuate the findings in women. We examined the association between LTPA quartiles and change in both relative and residual change in LTL during ten years of follow-up. In men, there were no significant associations between the LTPA quartiles and either the relative nor residual change of LTL (p for linearity 0.21 and 0.75, respectively) (Figure 10). In women, the association between LTPA quartiles was not significantly associated with relative change of LTL (p for linearity 0.071), but there was an association between LTPA quartiles and residual change of LTL (p for linearity 0.04) (Figure 10).

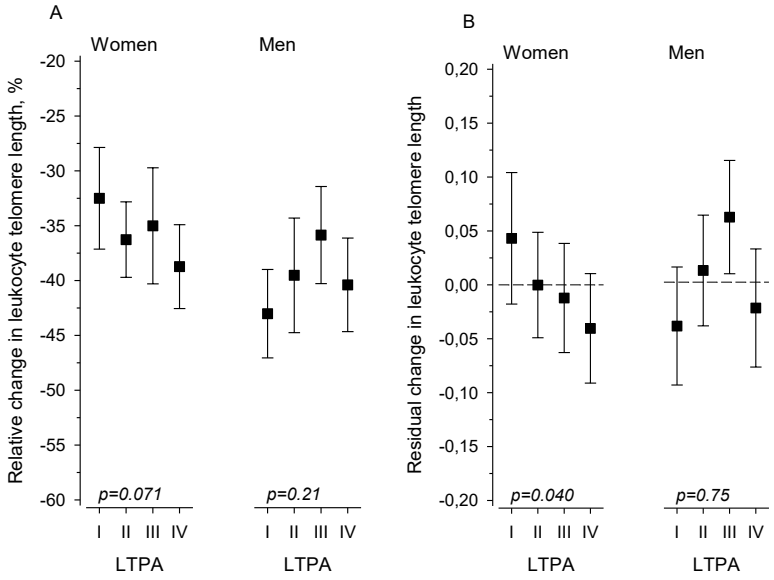

Figure 10 Relative change in leukocyte telomere length according to baseline leisure-time physical activity levels (LTPA) in women and men (A). Residual change in leucocyte telomere length according to baseline LTPA in women and men (B). Values were adjusted for age, educational attainment, smoking years, percentage of body fat, follow-up time and in women with estrogen exposure categorized in two groups (≤35 years and >35 years). Error bars indicate 95% confidence intervals. P-value indicates linearity. Reproduced with permission of the copyright owner Gerontology.

6 DISCUSSION

6.1 MAIN FINDINGS

Objectively measured physical activity was significantly associated with physical performance in this aging study population, both in men and women. Total physical activity, MVPA and light physical activity were associated with physical performance as assessed with SFT. Sedentary time was inversely associated with SFT results. Total volume of physical activity was significantly associated with all five individual test components of SFT used.

When men and women were divided into three categories based on their birth weight, we found that only in men with low birth weight the association between total volume of physical activity and physical performance was large. However, the association was significant in every birth weight group both in men and in women, but to a lesser degree.

We also investigated in this aging cohort the association between change in LTPA measured with a questionnaire and change in physical and mental components of HRQoL and symptoms of depression. We found in both genders that a change in total volume of LTPA was significantly associated with a positive change in the physical component of HRQoL. In women, change in total volume of LTPA was also associated with positive change in the mental component of HRQoL and with decreased depressive symptoms, but not in men.

In the study assessing LTPA and LTL we found that at baseline total volume of LTPA was not associated with LTL in older age in men or in women. In women baseline LTPA was associated with the residual change of LTL during ten years of follow-up, but not with the relative change of LTL. The residual change of LTL takes into account that the attrition rate of LTL is proportional to LTL at baseline. In men, there was not an association between LTPA at baseline and change in either relative or residual change of LTL.

6.2 INTERPRETATION OF THE RESULTS

6.2.1 PHYSICAL ACTIVITY AND PHYSICAL PERFORMANCE

In this aging cohort, objectively measured physical activity was associated with physical performance. Total physical activity, light physical activity and MVPA were all positively associated, and ST was inversely associated with the overall SFT score both in men and women. Similar to our findings a recent study has reported that accelerometer based MPVA was associated with performance-based functional tests (416). Yasunaga et al (416) also reported that replacing sedentary behaviour or light physical activity with MVPA was significantly and favourably associated with physical function measures. Their findings indicate that replacing even small amounts (such as 10 minutes) of sedentary behaviour and light physical activity with equal time of MVPA may contribute to improvements in older adults' physical function.

Another study (417) has shown that the effects of a long-term physical activity intervention versus health education was significantly higher on total SPPB score and 400m walking speed. SPPB includes four-meter gait speed, chair stand and balance tests. The fact that in the study of Santanasto et al (417) changes in chair-stand score explained a considerable portion of the effect of physical activity on the reduction of mobility disability and that the benefits of physical activity intervention compared with health education on the SPPB were more pronounced in older adults at highest risk for mobility disability, emphasise the importance of promoting physical activity also in elderly people. Physical activity interventions directly targeting lower muscle function and fitness could be especially effective at preventing mobility disability as preserving muscle strength seem to be important for good physical performance.

We used a modified test battery of SFT that consisted of five test components; chair stand test, arm curl test, chair sit and reach test, six-minute walk test and back scratch test. Total volume of physical activity was associated with all these five test components, but the association was strongest for the six-minute walk test. In accordance with our results, a pooled analysis of 27,220 older adults aged 65 years or older has shown that gait speed predicts

incidence of every day activity dependence, mobility difficulties and mortality (418). As another study has also shown that both slower gait speed at baseline and an accelerated decline in fast gait speed are associated with disability of older adults, measuring repeatedly gait speed of elderly could be a cheap and feasible way to identify those with higher risk of disability and offers a way for early prevention strategy (419).

Maintaining functional independence is important for both individuals and from a public health point of view as the number of older people continues to increase. There is emerging evidence that physical activity is one of the most important modifiable lifestyle factors in maintaining good health in old age (22). Cardiorespiratory capacity has shown to be a significant determinant of becoming dependent over an 8-year follow-up of older adults after accounting for age and presence of disease (420). There are strong evidence that physical decline during aging can be slowed down or prevented by promoting physical activity (421). At the same time with the age-related decline in functional capacity a sedentary lifestyle is increasing. A large proportion of older people are functioning close to the thresholds of physical ability to perform everyday activities. Sedentary behaviour has shown to be associated with disability in activities of daily living independent of time spent in MVPA (422). Sustained level of physical activity in older age has shown to be associated with improved overall health (423). But even more importantly Hamer et al (423) found that significant health benefits were also achieved among elderly people who did not become physically active until in old age. On the other hand, there are controversial results of the impact of LTPA on health of older people. Some studies has shown a favourable effect of LTPA on physical health and well-being in older adults (333, 424) while Yasunaga el al (416) found that only MVPA, not light physical activity, was significantly associated with older adults physical function and that replacing sedentary behaviour or light physical activity with MVPA was significantly associated with better physical functioning. Exercise interventions among elderly have also shown the advantageous effect of physical activity on physical functioning (425-427).

Physical activity influences physical functioning through several mechanisms. Physical activity has an impact on body composition by reducing

fat and increasing muscle mass and strength (428). Physical activity also increases or at least prevents the decline in bone mass (429). Physical activity increases aerobic capacity and is shown to be the most effective strategy for improving sarcopenia (430). As it also improves flexibility and balance, it therefore improves walking capacity and decreases risk of falling and related fractures (431). Physical activity also contributes to improved physical functioning by reducing the risk of several non-communicable diseases, such as several cancers, cardiovascular diseases and type 2 diabetes (7). Physical activity may also help older people to stay physically more active by reducing depression and cognitive disorders and by improving self-image and self-control (432-434).

In conclusion, physical activity is one of the most important, low-cost, easily achievable and modifiable health behaviours to maintain good physical functioning and therefore enabling longer independent life of elderly people.

6.2.2 PHYSICAL ACTIVITY AND PHYSICAL PERFORMANCE IN OLD AGE IN DIFFERENT BIRTH WEIGHT GROUPS

In this study including 695 aging people we found that the association between objectively measured physical activity and physical performance was dependent on body size at birth. When the study group was stratified by birth weight the volume of physical activity was significantly associated with physical performance in every birth weight group in both genders. However, we found that the association was large only in men whose birth weight was below 3000 g. There was no significant difference in the volume of physical activity between the birth weight groups. We also tested the different SFT test components and found that in men the association between volume of physical activity and all other test components than six-minute walk test was stronger in men with birth weight under 3000 g. In women, such consistency in the strength of the associations between different birth weight groups were not seen.

Low birth weight has previously shown to be associated with many adverse health outcomes, such as obesity (206), lower cardiopulmonary capacity (435) and with many non-communicable diseases (18). These conditions can be

linked to poor physical performance. Low birth weight has also been associated with lower muscle mass and strength (206) and also with altered composition and size of skeletal muscle fiber (205).

Fetal programming refers to the phenomenon where the environmental conditions during fetal development have an influence on the risk of diseases in later life (436). For example, insufficient nutrition during embryonic life can result in permanent alterations to certain structural and physiological metabolic functions of the fetus, which in turn increases the risk of several adverse health conditions. Low birth weight can be regarded as a surrogate marker of an adverse fetal environment. The fetus adapts to maternal malnutrition through changes in the production of fetal and placental hormones, and this results in delayed growth (437). During rapid growth in later pregnancy, if the nutrients are limited, the fetus attempts to protect key organs, especially the brain, to the detriment of other organs. Because the number of muscle fibers is determined at the time of birth (438), the intrauterine environment, in addition to the genetic component, is a major determinant of the muscle mass that is present in adult life (439, 440). Thus, unfavourable intrauterine environment that can result either from maternal nutrient restriction or placental insufficiency, restricts the muscle fiber number and can have permanent effects on the amount and size of muscle fibers (439). This leads to reduced muscle mass and strength throughout the life course. As the skeletal muscle mass decreases with age, the reduced muscle reservoir established at birth can accelerate the decline in physical performance in old age. The age-related muscle atrophy is fiber type specific, characterized by atrophy of type II (fast) fibers. In contrast, type I (slow) muscle fibers are largely unaffected (441). Muscle fiber subtypes are differentially sensitive to various external stimuli. Type I fibers are more susceptible to inactivity and denervation-induced atrophy, whereas type II fibers are more vulnerable to cancer cachexia, diabetes, chronic heart failure and aging (442). This fiber-specific atrophy appears to be due to different signalling pathways, and most of them are relevant to abnormality of protein degradation (442).

The amount of muscle mass is supposed to have an impact on fat deposition. A study performed in older men has shown that men with low birth weight had a higher percentage of body fat and fat mass but a lower fat-free soft tissue and muscle mass, and muscle-to-fat ratio and a higher trunk-to-limb fat ratio (443). This supports the concept that reduced capacity for muscle growth favours and accelerates visceral fat deposition and obesity.

The amount of muscle mass also contributes to insulin sensitivity. Skeletal muscle accounts for the majority of insulin-stimulated glucose uptake in the body (444). The myokines produced by muscle improve insulin sensitivity and stimulate energy consumption within adipose tissue (399). Thus, low muscle mass increases the risk to develop insulin resistance and type 2 diabetes.

We have shown that fetal circumstances can have long-term effects on health and these can be at least partly predicted by the birth weight of a new-born. According to our findings it could be suggested that men who were small at birth could have more advantage from physical activity in order to maintain higher level of physical functioning in later life.

6.2.3 PHYSICAL ACTIVITY AND HEALTH-RELATED QUALITY OF LIFE

We showed in a prospective study of 1036 aging people that positive changes in self-reported LTPA was associated with positive changes in the physical component of HRQoL in both genders during a ten-year follow-up period. When exploring the mental component of HRQoL, we found that only in women the positive change in LTPA was associated with positive change in the mental component of HRQoL and with reduction of depressive symptoms.

Our results are supported by many other studies. In accordance with our results Vagetti et al (277) found in a review exploring the association between physical activity and HRQoL that among older adults physical activity was positively and consistently associated with the physical domain of HRQoL and moderately associated with the mental domain of HRQoL. However, only two of the studies were longitudinal. Gouveia et al (344) has also shown in a recent cross-sectional study that physical activity, as explored by interview, was associated with both the physical and the mental component of HRQoL, but the association was stronger for the physical component. They also found that

BMI, body strength, aerobic endurance, depressive symptoms, falls and living alone were significant predictors of HRQoL and that positive relation of HRQoL to physical activity was significantly higher in old–old (70-79 years) compared to young-old adults (60-69 years) (344).

As many chronic conditions have been associated with poorer HRQoL (445, 446), we adjusted our analyses with a comorbidity score, but this actually did not attenuate our findings. In accordance with our findings, the study of Bertheussen and al (332) has shown a significant relationship between postal surveys based physical activity and HRQoL. In this study, frequency, duration and intensity of physical activity was significantly associated with both the physical and mental component of HRQoL in both genders and adjustment for self-reported presence of disease did not attenuate the results (332).

We found that only in women a positive change in LTPA was associated with diminished depressive symptoms. In line with our results, Zhang and Yen (447) have shown that physical activity ameliorated depressive symptoms among mildly and moderately depressed individuals in both genders, but this was seen most notably among depressed women. This study was done in middle-aged women, but there are also many cross-sectional studies done in older people that have reported a significant association between physical activity and diminished depressive symptoms. Salguero et al (340) have shown that physical activity was significantly associated with less symptoms of depression both in community-dwelling and institutionalized elderly. In contrast to our study, there were no difference between men and women. Joshi et al (272) has also shown that higher level of physical activity was associated with a lower risk of future depression but also that the type of physical activity seem to matter. In their study, sports and walking type of leisure-time activity provided the greatest benefit for mental health (272). In this study, as in many others, men and women were explored together. There are also interventional studies that support our results by showing the effect of physical activity on better HRQoL (321, 324). However, the interventions have been rather short, 2-12 months.

As many studies have demonstrated that psychological well-being is associated with reduced risk of cardiovascular disease, cognitive decline, and

mortality, Kim et al (448) wanted to explore if physical activity could be one mechanism behind the association between psychological well-being and better health outcomes. They found that higher baseline psychological well-being was associated with higher physical activity levels over 11 years, with a slower rate of decline in physical activity among people who were active at baseline and increasing physical activity among people who were inactive at baseline (448). Also, in this study the results were not significantly attenuated after adjustment for health status and depression, suggesting that the associations were independent of these factors.

Higher level of physical activity has been shown to be associated with a decreased risk of obesity and many non-communicable diseases (7). Engaging more in physical activity has also been shown to be associated with better aerobic capacity and to prevent falls (449, 450). These influences can lead to better functional capacity. Physical activity has also been shown to be associated with decreased cognitive decline and incidence of mental disorders and it can directly have an influence on self-efficiency (9, 451). These effects can result in improved HRQoL.

There are several regions of the brain that have shown consistent volumetric reductions in depression. Many of these regions also show structural plasticity in response to exercise or in relation to higher levels of fitness (452). It has been speculated that exercise exerts its anti-depressant effects partially through these neural pathways (453). Exercise and antidepressant medication have shown to trigger similar neuromolecular changes and also to have overlapping regional effects on brain structure (452, 454). Thus, physical activity can be regarded as a non-pharmaceutical treatment for depression.

6.2.4 PHYSICAL ACTIVITY AND LEUCOCYTE TELOMERE LENGTH

We explored in an aging cohort of 1014 individuals the association between LTPA and LTL at baseline and with the change in LTL during 10 years of follow-up. We found that the volume of LTPA was not significantly associated with LTL at baseline in either sex. We also showed that during ten-year follow-up, the volume of LTPA at baseline was not significantly associated with the

change of LTL in men. However, in women, volume of LTPA at baseline was associated with greater shortening of LTL during the follow-up period. The relationship between LTPA and change in LTL in women was stronger in analyses using residual change of LTL, taking into account the actuality that the rate of LTL shortening was proportional to LTL at baseline (455).

Studies that have not been restricted to older adults have shown that physical activity is significantly associated with LTL both in men and women. Tucker (371) found that adults (men and women ages 20-84 years) with high level of self-reported physical activity had significantly longer LTL than their more sedentary counterparts. Ogawa et al (372) have shown in the same study cohort that vigorous LTPA was associated with longer LTL, but neither transportation/commuting physical activity or moderate LTPA was significantly associated with LTL. Also, Cherkas et al (456) have shown that LTL was positively associated with increasing LTPA level in a study group compromising of men and women aged 18-81 years.

In contrast to our study, Shadyab et al (457) have shown in a cross-sectional study that older women participating in greater amounts of total LTPA and MVPA had longer LTL. The fact that they used Southern blot when measuring the LTL and that the average age of the study group was almost 20 years older compared to our study group could explain at least partly the different result at baseline. In addition, Shadyab et al (457) found that the association of total LTPA with LTL was significant only when comparing the highest with the lowest total physical activity quartiles. Shadyab et al (370) have explored in the same study cohort of older women cross-sectional associations between accelerometer-measured total, light, and MVPA and LTL. They found that women engaging in higher amount of MVPA had significantly longer LTL. Also, total physical activity was associated with longer LTL, but light physical activity was not significantly associated with LTL. However, after adjusting for health-related factors, findings were not significant.

There are only a few longitudinal studies done among older adults exploring the association between physical activity and LTL. Soares-Miranda et al (376) found in a study among older adults (age 73 years on average at baseline) that cross-sectionally only greater walking distance, but not other

physical activity measures was associated with longer LTL. In longitudinal analyses, no significant associations were observed between baseline physical activity and change in LTL, but change in LTPA was inversely associated with change in LTL (376). In contrast to our study telomere length was measured using the Southern blot method and men and women were analyses together.

In our study LTPA was not associated cross-sectionally or longitudinally with the change in LTL in men. In accordance with this result there are also a few studies done in older people showing no significant association between physical activity and LTL. Woo et al (373) did not find in an older Chinese population (mean age 72,8 for men and 72,0 for women) a significant difference in LTL across quartiles of physical activity in men or in women.

Since one study (458) has reported that women with the longest LTL underwent menopause three years later than those with the shortest LTL, we adjusted our analyses with length of reproductive life and hormone replacement therapy.

Overall, the association between physical activity and LTL has shown to be inconsistent, which may be explained by the differences in the age, characteristics and race of study groups and methods used to assess physical activity and to measure LTL.

The mechanism explaining how physical activity is associated with LTL may be due to several different mechanisms. Physical activity is known to have anti-oxidant and anti-inflammatory influences (459) and this could slow down the attrition rate of telomeres (366). Chronic physical activity has been shown to suppress inflammation and oxidative stress (393, 395), but an acute session of physical activity increases the oxidative process (460, 461). It has been shown that a single bout of exercise induces oxidative stress but also increases antioxidant enzyme activity (462). One study has shown that acute exercise increased resistance to oxidative stress in young but not older adults (461) which suggests that signal transduction of acute exercise may be impaired with aging. Physical activity has also been shown to stimulate the activity of telomerase (463), a reverse transcriptase enzyme, that elongates telomere length (464) and to upregulate messenger RNA expression of telomerase reverse transcriptase (465). When telomeres have shortened to a critical

length, cell cycle arrest is induced and somatic cells will permanently stop dividing and enter senescence (466). Senescence of human cells has been shown to be related to in addition to shorter telomeres also to dysfunctional mitochondria, which are the main source of ROS (467). Overproduction of ROS results in oxidative stress, which can lead to oxidation of biomolecules and chronic oxidative stress, that is one of the leading causes of many diseases and chronic inflammation. Inflammation causes accelerated white blood cell turnover and additional telomere attrition resulting in accelerated aging. Telomere dysfunction is associated with impaired mitochondrial biogenesis and function by activating p53 which represses peroxisome proliferator-activated receptor gamma, coactivator 1 alpha and beta (PGC-1α and PGC-1β) and leads to cellular growth arrest, senescence and apoptosis (415). Dysfunctional mitochondria increases ROS production and decreases ROS-detoxifying enzymes which cause additional damage both to mitochondrial and genomic DNA, including telomeres (468). Lack of exercise contributes to increased ROS production and regular moderate exercise again diminishes ROS production, preserves telomeres and reduces mitochondrial damage (468).

In our study the association between physical activity and LTL was gender specific and this can at least partly be explained by the fact that telomere dynamics has been shown to differ between men and women. A recent trial has shown that an acute exercise session induced a significant response in the catalytic subunit of the telomerase, hTERT, in the cohort as a whole, but the response was significantly greater in men compared to women (469). Furthermore, women have been shown to have longer telomeres (364) and the rate of LTL shortening tend to be slower in women than in men (470). LTL was longer in women than in men also in our study, but in contrast to previous studies there was no difference in the attrition rate of LTL between genders. Estrogen has antioxidant effects and has been shown to promote the expression and activity of telomerase (365). This can be one explanation for the difference in telomere dynamics between the genders.

It is possible that obesity mediates the relationship between physical activity and LTL as obesity has been associated with shorter LTL (471). In our

study cohort, women with lower body fat percentage had greater volume of LTPA. Otherwise, there were no statistically significant differences in the characteristics between the LTPA groups either in men or women.

6.3 METHODOLOGICAL CONSIDERATIONS

The HBCS is globally a unique birth cohort study including 13 345 subjects in the epidemiological part of the cohort and over 2000 randomly selected subjects in the clinical part. The HBCS has been made possible by the unique child welfare and school healthcare system in Finland. It has been possible to abstract data from birth records, child welfare clinic and school healthcare records. Data on growth, socioeconomic aspects and general health have been collected. The clinical study cohort is longitudinal with data throughout the life course including prenatal life, early childhood and later life. The study cohort has been followed up clinically and extensive data has been collected including metabolic and dietary data, other lifestyle data including physical activity and psychological factors. There is also a long tradition of population registration in Finland and this has made possible to obtain data from national health care registers and data from Statistics Finland.

In study I and II we used a test battery consisting of five physical fitness test components instead of a single test in order to get a more comprehensive insight of the physical performance. Previous studies showing a positive association between physical activity and physical performance in old age have used a more concise physical fitness test, e.g. hand grip, gaits speed or SPPB (472, 473). The SFT we used is a validated and reliable physical fitness test and it is specially designed for older adults (242). It measures strength, endurance, agility, flexibility and balance and these all capabilities are associated with the maintenance of physical independence in old age (474-476).

In study I and II physical activity was measured objectively and in study III and IV with a questionnaire. We measured the volume of physical activity objectively with a body-worn monitoring and it may give more reliable information about the volume of physical activity in an older study cohort (405). The SWA is shown to be valid in assessing EE in free-living conditions.

EE estimated by the SWA correlates with estimates from doubly labelled water and indirect calorimetry also in a study performed in elderly people ($r = 0.48$, $p<0.01$) (405). In another study (477), the accuracy of TEE and activity energy expenditure (AEE) estimates from the SenseWear Pro armband were assessed by comparing TEE and AEE assessed by doubly labelled water and indirect calorimetry. AEE was calculated as 0.9 TEE – RMR. Both TEE and AEE were highly correlated with SWA 5.1 ($r = 0.901$, $p < 0.001$ and $r = 0.786$, $p < 0.001$). Anyway, a study (478) done among nursing home residents (mean age = 85.5 ± 5.5 yr) has shown that even if EE estimated with SWA was high correlated with EE estimated with indirect calorimetry (portable gas analyser, Oxycon Mobile) (r sitting = 0.68, activity tasks = 0.88) SWA significantly underestimated EE, with an overall absolute percent error of 14.1% ± 7.9%. The largest absolute percent differences were observed during sitting periods compared with activity tasks ($p < 0.05$). A recent study (479) has validated the SWA in children, adolescents, and adults using indirect calorimetry as reference for energy expenditure. The overall mean absolute percent error with SWA5.2 was 24% in children, 23% in adolescents, and 20% in adults. The error was larger for sitting and standing (23%-32%) and for basketball and biking (19%-35%), compared to walking and running (8%-20%). In general, SWA underestimated energy expenditure. Underestimation seemed to appear above intensities corresponding to a running speed above 9 km·h−1 and a MET value of 10 METs, but such high intensities are rare in older population. We used pre-defined cut-off points when we divided the physical activity to different physical activity intensity categories. We did not adjust the intensity of physical activity to each participants maximal capacity. Persons at same age can differ markedly in maximal cardiorespiratory capacity and also in respond to an exercise challenge (480). To get more accurate assessment of one's physical activity level, relative intensity of physical activity should be used (38). It takes into account such variation by adjusting the intensity relative to person's maximal capacity. An exercise intensity of certain level might be a warm-up for one person but requires a maximal effort by another.

Questionnaires are more suitable in epidemiological studies as being low-cost and more convenient, but especially among older people they are prone

to recall bias due to cognitive impairments (77, 405). Also compared to accelerometer-measured physical activity questionnaires based physical activity tend to overestimate physical activity levels (481). These self-reported errors in measuring the volume of physical activity can lead to attenuation in the strength of reported association between physical activity and health outcomes. In assessing the self-reported LTPA we used the KIHD questionnaire, which has been modified from the Minnesota Leisure Time Physical Activity Questionnaire (Minnesota LTA). Goran and Poehlman (482) have shown double labelled water (DLW) and the Minnesota LTA to have a strong correlation in a study of 13 older men and women ($r = 0.83$, $p < 0.0001$). On the other hand, in the study of Starling et al (483), the Minnesota LTA underestimated daily physical activity by ~50–60% compared with DLW both in older men and women. The advantages of the KIHD questionnaire we used includes that it collects data from a longer time period (the previous 12 months) and it also provides information about the intensity, duration and type of physical activity.

Most objective monitors have the capability to capture the intensity and volume of activity, but their ability to capture the type of activity is limited. With self-report instruments it is also possible to capture the type and reason of activity. It is important that also lower volumes of physical activity are detected, especially in older adults who tend to engage more in lower-intensity activities (484). Questionnaires have shown not to be as accurate in assessing low intensity activities than vigorous activities in older adults (485). With multiple sensor activity devices, like the SWA, it is possible to assess accurately PAEE and also to capture information about the intensity, duration and frequency of activity (76).

In study III we used validated questionnaires, SF-36 and BDI, to assess HRQoL and depressive symptoms. SF-36 is the most widely used instrument measuring HRQoL in population based research (486). It is a practical, reliable, and valid measure of physical and mental health also in older populations (487). BDI has been shown to be a reliable and valid screening instrument for depression also among older adults (488, 489).

In study IV we measured the relative telomere length from leucocytes using real-time quantitative PCR. This method is inexpensive, fast and requires only a small amount of DNA and is therefore suitable for epidemiological studies. Using a quantitative PCR method for measuring LTL has relatively high inter-assay variability and it may not be the gold-standard for assessment of telomere length, although it may be the most common method used (490). The Southern blot method is considered the gold standard and it provides LTL in kilobases, unlike qPCR methods that provide a ratio of telomeric DNA content (358).

Study III and IV were longitudinal and the follow-up time was long and the LTPA, HRQoL and depression symptoms were measured with the same questionnaires.

The limitations of HBSC include that cohort members may not represent all citizens in Finland as they were both born and attended child-welfare clinics in the city of Helsinki. Also, the study population of the clinical part of the cohort lived in the surroundings of Helsinki, the capital of Finland, and may not be fully representative of all older people in Finland. As some of the individuals included in this cohort were born during the Second World War, families might have suffered from food shortages. These results might have been affected also by a survival effect among those with better physical performance.

The setting in study I and II were cross-sectional and therefor the direction of causality is uncertain. It is possible that those with poorer physical performance were not able to be physically active. But since there is large evidence of the importance of physical activity in maintaining good physical performance it supports our interpretation of the result (264, 421). Cohort members who had severe functional limitations may have been excluded from the study as participating in the SFT requires a certain level of physical fitness. Our study may also be limited by the "volunteer effect", because not everyone from the original cohort was willing to participate in the fitness test or use the activity monitor.

In studies III and IV the setting was longitudinal and also in these the direction of causality is uncertain. Cohort members with a better health may

have been able to engage more in physical activity. There might be a selection bias too. In study III and IV only those who were in better shape might have attended the follow-up examinations. Also, there might be a survival effect in study IV. Shorter LTL have been associated with premature mortality (491), which might have had an influence on the survival and inclusion of the cohort members with shorter LTL.

6.4 CONCLUSIONS AND FUTURE DIRECTIONS

The present study shows that physical activity has an influence on how the later years of life will be. The first part of the study shows a strong association between the volume of physical activity and physical performance among older people. Even if this cross-sectional study was not able to indicate a causal relationship between physical activity and physical performance, it can be hypothesized that by enhancing physical activity among older people we will be able to increase independent years of life due to improved physical fitness and compressed morbidity. As cardiorespiratory fitness has been shown to predict even better the risks of coronary heart disease and cardiovascular disease than the volume of physical activity (247, 492), it can be postulated if there should be more studies exploring the association between cardiorespiratory fitness rather than physical activity level and effects on health. Also, cardiorespiratory fitness and the response of exercise are largely heritable and thus also the health consequences are supposed to be at least to some degree.

As the prenatal period has been shown to influence the health and wellbeing in later life and birth weight can be regarded as a surrogate of fetal environment, we explored how birth weight modulates the association between physical activity and physical performance. We found this association to be strongest in men with low birth weight. Our results are in line with the DOHaD hypothesis proposing that the prenatal period can have long-term effects on health that can be predicted partly by body size at birth. According to our findings it could be proposed that especially those born with low birth weight might benefit engaging in physical activity in order to preserve their

physical functioning in old age. In conclusion, our study supports the importance of physical activity in maintaining good physical performance among older people.

In the longitudinal study exploring the association between change in physical activity and HRQoL in later life, we found that more positive changes in LTPA during a ten-year follow-up period was associated with positive changes in the physical component of SF-36 in both men and women. In men, we did not find a significant association between change in LTPA and change in the mental component of SF-36 or symptoms of depression. However, in women there was a significant positive association between positive change in LTPA and the mental component of SF-36 and an inverse association with depressive symptoms. According to our findings it can be postulated that an increase in physical activity even in later years can have a positive influence on HRQoL of older adults. HRQoL has a remarkable role in healthy aging.

In the study exploring the association between physical activity and LTL, we found this association to be still contradictory. We did not find a significant association between LTPA and LTL in either gender. During the ten-year follow-up LTPA in baseline was not significantly associated with change in LTL in men, but in women there was an inverse association. According to our findings the association between physical activity and LTL shortening during late adulthood is sex dependent, but further studies are, however, needed to assess the relationship between the physical activity and LTL among older people. It is possible that in future there may be more exact methods to measure the LTL and the possible relationship between physical activity and LTL might be clarified.

As the number of aging people is increasing, preserving good health and maintaining physical independence becomes an important issue. Promoting physical activity among older people can be regarded crucial in order to preserve physical functioning, to enable independent life as long as possible, to preserve quality of life and to compress morbidity. According to WHO in order to improve cardiorespiratory and muscular fitness, bone and functional health, reduce the risk of non-communicable diseases, depression and cognitive decline, older adults should do at least 150 minutes of moderate-

intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity. In addition, they should do muscle-strengthening activities 2 or more days a week. Also, older adults, with poor mobility, should perform physical activity to enhance balance and prevent falls on 3 or more days per week and when older adults cannot do the recommended amounts of physical activity due to health conditions, they should be as physically active as their abilities and conditions allow. The very recent Finnish recommendation for health-enhancing physical activity for adults over 65 years by UKK institute also emphasizes muscle-strengthening and balance-enhancing physical activity for older adults. It highlights also the importance of diverse physical activity in order to cope with daily tasks, preserve or improve functional capacity and prevent falls. The recommendation emphasizes the importance of all light physical activity every moment it is possible, to take breaks of being stationary and sufficient sleep. It has also abandoned the idea of at least 10 minutes bouts of physical activity, replaced with the fact that every minute of even seconds of physical activity have benefits to health. Physical activity is an easily modifiable health behaviour, but older people can have mental and physical obstacles participating in physical activities. There is a great need for actions to help older people to fulfil the physical activity demands. A study has shown that exercise training improves exercise capacity to a greater degree in older adults than the young (493). Older adults were not able to increase their peak oxygen consumption to the same degree as the young, but this was counteracted by the fact that improvements in exercise efficiency, oxygen debt and recovery kinetics were even greater in the older subjects than in the young. This endorses the importance of regular physical activity participation also in old age.

According to the Finnish Best Clinical Practise of health-enhancing physical activity guidelines, most of the chronic diseases of elderly are a reason for participating in regular physical activity rather than a barrier. Physical activity is an easily modifiable health behaviour within reach of everyone and has a very low risk when correctly implemented. As there are a lot of evidence

on the positive influence of physical activity in preventing many chronic diseases and conditions associated with old age, promoting physical activity among older people should be prioritized in future.

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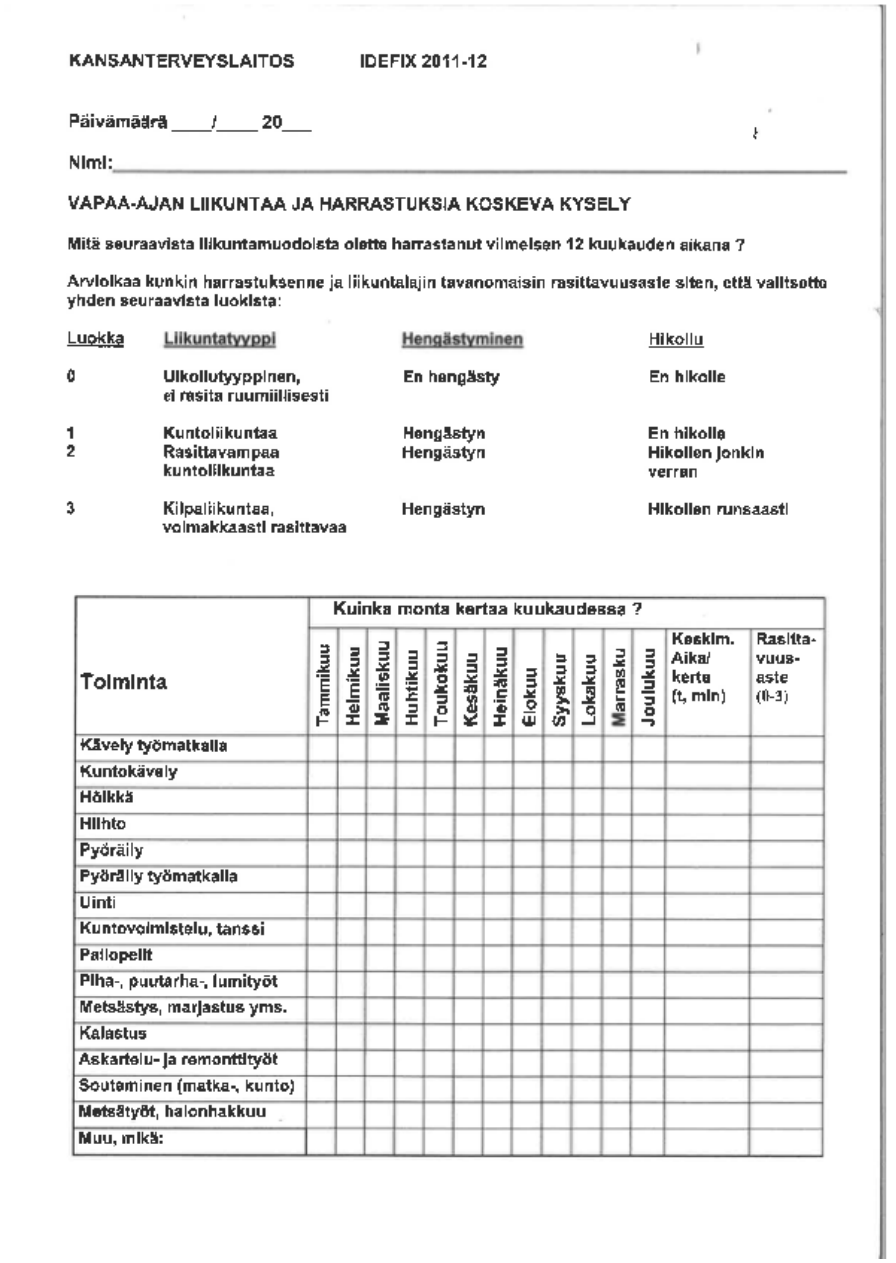
Espoo, April 2020

Hanna Jantunen

APPENDICES



KANSANTERVEYSLAITOS IDEFIX 2011-12

Päivämäärä ____/____ 20___

Nimi:_____

VAPAA-AJAN LIIKUNTAA JA HARRASTUKSIA KOSKEVA KYSELY

Mitä seuraavista liikuntamuodoista olette harrastanut viimeisen 12 kuukauden aikana ?

Arvioikaa kunkin harrastuksenne ja liikuntalajin tavanomaisin rasittavuusaste siten, että valitsette yhden seuraavista luokista:

Luokka	Liikuntatyyppi	Hengästyminen	Hikoilu
0	Ulkoilutyyppinen, ei rasita ruumiillisesti	En hengästy	En hikoile
1	Kuntoliikuntaa	Hengästyn	En hikoile
2	Rasittavampaa kuntoliikuntaa	Hengästyn	Hikoilen jonkin verran
3	Kilpaliikuntaa, voimakkaasti rasittavaa	Hengästyn	Hikoilen runsaasti

Toiminta	Kuinka monta kertaa kuukaudessa ?												Keskim. Aika/ kerta (t, min)	Rasitta-vuus-aste (0-3)
	Tammikuu	Helmikuu	Maaliskuu	Huhtikuu	Toukokuu	Kesäkuu	Heinäkuu	Elokuu	Syyskuu	Lokakuu	Marraskuu	Joulukuu		
Kävely työmatkalla														
Kuntokävely														
Hölkkä														
Hiihto														
Pyöräily														
Pyöräily työmatkalla														
Uinti														
Kuntovoimistelu, tanssi														
Pallopelit														
Piha-, puutarha-, lumityöt														
Metsästys, marjastus yms.														
Kalastus														
Askartelu- ja remonttityöt														
Soutaminen (matka-, kunto)														
Metsätyöt, halonhakkuu														
Muu, mikä:														

Figure 11 12 kuukauden vapaa-ajan liikuntaa ja harrastuksia koskeva kysely.

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